

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203255Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203255

SUPPL # N/A

HFD # 510

Trade Name Signifor LAR

Generic Name (pasireotide) for injectable suspension, for intramuscular use

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known December 15, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES **X** NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES **X** NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO **X**

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO **X**

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO **X**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO **X**

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study CSOM230C2305: "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs octreotide LAR in patients with active acromegaly"

Study CSOM230C2402: "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO **X**

Investigation #2 YES NO **X**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO **X**

Investigation #2 YES NO **X**

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study CSOM230C2305: "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs octreotide LAR in patients with active acromegaly"

Study CSOM230C2402: "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 074642 YES **X** ! NO
! Explain:

Investigation #2
IND # 074642 YES **X** !
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES !
! NO
Explain: ! Explain:

Investigation #2
YES !
! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO **X**

If yes, explain:

N/A

Name of person completing form: Jennifer Johnson

Title: Regulatory Health Project Manager

Date: December 15, 2014

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.

Title: Division Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12;

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

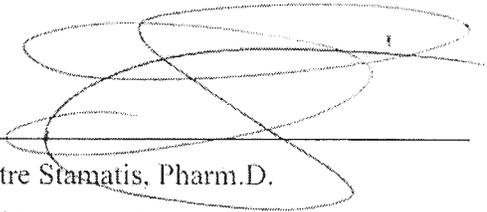
/s/

PAMELA LUCARELLI
12/15/2014

JEAN-MARC P GUETTIER
12/15/2014

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Demetre Stamatis, Pharm.D.
Global Program Regulatory Manager
Drug Regulatory Affairs

October 21, 2013

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 203255 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>						
Proprietary Name: Signifor LAR Established/Proper Name: pasireotide Dosage Form: intramuscular injection		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A						
RPM: Jennifer Johnson		Division: Division of Metabolism and Endocrinology Products						
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>						
\ Actions <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%; vertical-align: top;"> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 15, 2014</u> • Previous actions <i>(specify type and date for each action taken)</i> </td> <td style="width: 30%; vertical-align: top; border-left: 1px solid black;"> <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR </td> </tr> <tr> <td style="vertical-align: top;"> ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ </td> <td style="vertical-align: top; border-left: 1px solid black;"> <input type="checkbox"/> Received </td> </tr> <tr> <td style="vertical-align: top;"> ❖ Application Characteristics³ </td> <td style="border-left: 1px solid black;"></td> </tr> </table>			<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 15, 2014</u> • Previous actions <i>(specify type and date for each action taken)</i> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received	❖ Application Characteristics ³	
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 15, 2014</u> • Previous actions <i>(specify type and date for each action taken)</i> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR							
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	<input type="checkbox"/> Received							
❖ Application Characteristics ³								

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 5
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes N/A
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	December 15, 2014 (Approval)
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Refer to labeling attached to approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Not needed; refer to labeling attached to approval letter
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Refer to labeling attached to approval letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Not needed; refer to labeling attached to approval letter
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Refer to labels attached to approval letter
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	January 27, 2014 January 22, 2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: January 27, 2014 DMEPA: March 28, 2014 DMPP/PLT: December 12, 2014 OPDP: <input checked="" type="checkbox"/> None SEALD: August 20, 2014 CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	January 15, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <i>PeRC review not necessary because this active moiety (pasireotide) was granted orphan designation status for the treatment of acromegaly on August 25, 2009</i> 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	December 2 and 16, 2013; January 24 and 28, March 17 and 25, April 23, May 12, 16, 28 and 29, June 11, July 1, 14, 17, 21, August 15, 18, 19, 25, 27, September 2, November 5, 17, 26, December 11 and 15 (2), 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	X N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	November 29, 2011
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	October 15, 2007
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	X N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	X N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	Type C Guidance Meeting on September 9, 2013 (follow-up to Pre-NDA meeting held on November 29, 2011)
❖ Advisory Committee Meeting(s)	X No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	X None
Division Director Summary Review (<i>indicate date for each review</i>)	December 15, 2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	December 15, 2014
PMR/PMC Development Templates (<i>indicate total number</i>)	X None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	X No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	January 3 and September 2, 2014
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See pages 15-16 of Clinical review dated September 2, 2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	IRT-QT review: July 17, 2014

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A August 8, 2014 (REMS not needed)
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	OSI Clinical Inspection Review Summary: July 21, 2014; OSI letters to investigators: July 30, August 22, September 18 (4), 2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	January 8 and August 11, 2014
Clinical Pharmacology <input type="checkbox"/> None	
Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	August 15, 2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	X No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	January 6, April 4 and August 1, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc (Reviewed under NDA 200677, Signifor)
❖ ECAC/CAC report/memo of meeting	X None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		ONDQA reviews: January 6 and August 11, 2014; ONDQA biopharmaceutics reviews: August 11 and September 5, 2014
❖ Microbiology Reviews		<input type="checkbox"/> Not needed December 3, 2013; August 21, 2014
X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		CDRH consult reviews: January 3, 2014 (device) August 19, 2014 (human factors) October 8, 2014 (device) December 8, 2014 (Office of Compliance/Division of Manufacturing & Quality)
❖ Environmental Assessment (check one) (original and supplemental applications)		
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Refer to page 151 of ONDQA review dated August 11, 2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
X NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: October 28, 2014 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	X Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	X Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	X Done
❖ Ensure Pediatric Record is accurate	X Done
❖ Send approval email within one business day to CDER-APPROVALS	X Done

Johnson, Jennifer

From: ees_admin@fda.gov
Sent: Tuesday, August 26, 2014 11:12 PM
To: Godwin, Francis; Johnson, Jennifer; Salganik, Maria*; Spain, Nancy *; Kumar, Priyanka; Kasliwal, Ravindra K; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 203255/000 Decision: PENDING, Decision Date: 08/26/2014, Re-evaluation Date:

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov).

To contact the EES technical staff, send an email to CDER EES Help (EESHHELP@fda.hhs.gov). Thank you.

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/s/

MARY GRACE LUBAO
12/24/2014

From: [Gao, Rose](#)
To: [Johnson, Jennifer](#)
Subject: RE: NDA 203255 (Signifor LAR): Final agreed-upon labeling
Date: Monday, December 15, 2014 10:33:56 PM

Dear Jennifer,

I confirm the receipt of PI, PPI and demo IFU. They look good. Thank you!

Best Regards

Rose Gao
Director Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
Building 315, 4th Floor
East Hanover, NJ 07936-1080
Phone +1 8627786795
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Fax +1 9737818545
rose.gao@novartis.com
www.novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Monday, December 15, 2014 10:23 PM
To: Gao, Rose
Subject: NDA 203255 (Signifor LAR): Final agreed-upon labeling

Dear Rose,

Please find attached the final PI, PPI and demonstration kit instructions for NDA 203255, Signifor LAR (pasireotide) for intramuscular injection, for intramuscular use. These pieces of labeling will be attached to the action letter.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

PAMELA LUCARELLI
12/15/2014

From: [Gao, Rose](#)
To: [Johnson, Jennifer](#)
Subject: RE: NDA 203255 (Signifor LAR): Final agreed-upon packaging
Date: Monday, December 15, 2014 7:58:10 PM

Dear Jennifer,
Many thanks for the final agreed packaging labels. I confirm receipt. They look good.

Best Regards

Rose Gao
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rose.gao@novartis.com
www.novartis.com

From: Johnson, Jennifer [mailto:Jennifer.Johnson@fda.hhs.gov]
Sent: Monday, December 15, 2014 7:11 PM
To: Gao, Rose
Subject: NDA 203255 (Signifor LAR): Final agreed-upon packaging

Dear Rose,

Please find attached the packaging for NDA 203255, Signifor LAR:

- Revised vial labels (trade and demonstration kit) submitted to me via email on August 29, 2014
- Revised syringe labels (trade and demonstration kit) submitted to me via email on September 11, 2014
- Revised tray labels (trade and demonstration kit) submitted to me via email on August 29, 2014
- Revised carton labels (trade) submitted to me via email on August 29, 2014
- Revised demonstration kit carton label submitted to me via email on November 7, 2014

We have reviewed your revised labels, and find them acceptable.
Please confirm receipt and final agreement on the Signifor LAR packaging.
Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson

Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

PAMELA LUCARELLI
12/15/2014

From: Johnson, Jennifer
To: ["Gao, Rose"](#)
Cc: [Ganeshan, Shanthi](#)
Bcc: [Johnson, Jennifer](#)
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments - *Latest FDA edits/comments*
Date: Wednesday, December 10, 2014 1:50:00 PM
Attachments: [FDA Round 3 edits to Signifor LAR NVS 10 Dec 2014.doc](#)

Dear Rose,

Thank you for your time during our call earlier, and to your team during yesterday's TC. Please find attached the latest FDA draft of the PI, with further changes incorporated per yesterday's discussion.

Note: since the patient information is currently being reviewed by DMEP and the Patient Labeling Team, I have extracted it from this document and will re-insert it after the review is complete.

Also, see our comment in response to yours regarding the Instruction Booklet at the end. We do not agree that it is necessary to duplicate the information already included in Section 2, since the healthcare provider will receive the PI; therefore, we recommend deleting the standalone instruction booklet.

Regarding your request to schedule another TC for tomorrow in case it is needed, I am discussing this with Dr. Guettier and will get back to you.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
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jennifer.johnson@fda.hhs.gov

From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Tuesday, December 09, 2014 8:38 PM
To: Johnson, Jennifer
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Jennifer,
Thank you for organizing today's TC.

As we discussed in today's meeting, with anticipating FDA next round of PI comments today, our team will try our best to respond by this Thursday (morning). Since we are very close to the action date, can we schedule another meeting Thursday afternoon or Friday morning with FDA to resolve any outstanding issues?

Please keep posted with the FDA next round of PI comments. I am going home now and I will check email later tonight.

Best Regards

Rose Gao
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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Tuesday, December 09, 2014 12:14 PM
To: Gao, Rose
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Rose,

Thank you for sending the list of Novartis attendees – we look forward to discussing with your team this afternoon.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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jennifer.johnson@fda.hhs.gov

From: Gao, Rose [<mailto:rose.gao@novartis.com>]
Sent: Monday, December 08, 2014 11:24 PM

To: Johnson, Jennifer
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Jennifer,

Thank you for the list of FDA attendees. Please find below for NVS participant lists for the Dec 9 TC meeting.

Shanthi Ganeshan, Ph.D., North America Region Head Drug Regulatory Affairs
Rose Gao, MS, Director, Drug Regulatory Affairs
Geromo Gericke, M.D., Global Program Head Oncology
Sophie Jauffret, Ph.D., Biostatistics Group Head, GPT SOM/LCI BDM
Sibylle Jennings, Ph.D., Global Program Regulatory Director
William Ludlam, M.D., Director Clinical Research, US CDMA-Rare Disease II
Shoba Ravichandran, M.D., Executive Director Clinical Research

If there is any updates to the list, I will let you know.

Best Regards

Rose Gao
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Fax +1 9737818545
rose.gao@novartis.com
www.novartis.com

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Monday, December 08, 2014 11:26 AM
To: Gao, Rose
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Rose,

Thank you for promptly providing the TC dial-in info.

For this TC, we plan on having the following attendees, in addition to myself:
Jean-Marc Guettier – division director
Smita Abraham – clinical reviewer
Jennifer Clark – statistical reviewer

Mark Rothmann – statistics team leader
Pam Lucarelli – chief, project management staff (my supervisor – optional)

If there are any changes to this plan, I will let you know.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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Office of Drug Evaluation II
Center for Drug Evaluation and Research
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jennifer.johnson@fda.hhs.gov

From: Gao, Rose [<mailto:rose.gao@novartis.com>]
Sent: Monday, December 08, 2014 11:04 AM
To: Johnson, Jennifer
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Jennifer,

Thank you for getting back to me. Our team will be available at proposed time (Tuesday Dec 9th, 2:20 pm EST).

Could you please let me know who in your team will be attending this TC, so that I can make sure that appropriate people in our team will be attending this meeting.

Please also see below TC dial-in information.

Teleconference Information

Participant Passcode:  (b) (4)

*Please use your nearest dial in and **avoid toll free numbers if dialing from Novartis phones to reduce costs.***

United States (toll)  (b) (4)
United States (toll free) 
Switzerland (toll free) 
Switzerland, Zurich (local) 
Germany (local) 
Local - Germany, Frankfurt 
Local - Germany, Munich: 
Local - Sweden, Stockholm 

Additional Dial-In-Numbers: [View a List](#)

Best Regards

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www.novartis.com

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Monday, December 08, 2014 10:58 AM
To: Gao, Rose
Cc: Ganeshan, Shanthi
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Rose,

Thank you very much – we are reviewing the PI now.

As I mentioned before, I scheduled a teleconference for tomorrow (Tues Dec 9th) at 2:20 pm EST. (We will be having internal discussion first beginning at 2:00.)

Could you please provide TC dial-in information?

Kind Regards,
Jennifer

Jennifer Johnson
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jennifer.johnson@fda.hhs.gov

From: Gao, Rose [<mailto:rose.gao@novartis.com>]
Sent: Friday, December 05, 2014 5:46 PM
To: Johnson, Jennifer
Subject: RE: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Jennifer,

To follow up with the email sent by Shanthi yesterday, please find attached FDA clean PI with Novartis's proposed revisions and rationale and along with our response document to further

support some of revisions. Please let me know if you have any questions and we will be in touch for scheduling the TC next week. Many thanks!

Best Regards

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From: Ganeshan, Shanthi
Sent: Thursday, December 04, 2014 3:01 PM
To: Jennifer.Johnson@fda.hhs.gov
Cc: jean-marc.guettier@fda.hhs.gov; Gao, Rose
Subject: NDA 203255 - Signifor LAR/Acromegaly Label comments

Dear Jennifer,

Thanks for speaking with us regarding the Signifor LAR draft FDA label proposal. The team is getting ready to provide our response tomorrow, as requested by the division.

Novartis is in agreement to majority of the Agency's revisions, however, since we have limited time before the action date, I thought it would be efficient to give you some high level outline of the main changes to the revised FDA label, to streamline the label discussions as much as possible.

The main areas where we are still seeking alignment with the Agency are as follows:

1) Efficacy

- a. We acknowledge the need for a disclaimer in the clinical trial section that the maximum dose of octreotide acetate for injectable suspension of 40 mg approved for use in the United States was not used in this trial because the trial was multi-national and the 40 mg dose was not approved in all participating countries.
- b. We would like to further understand the rationale for the statement (b) (4)
[REDACTED]
 - i. The study design was discussed and agreed with FDA at the EoP2 meeting
 - ii. We strongly believe that the p-values need to be included in the results tables with the appropriate limitations as this information is critical to demonstrate the robustness of the trials. Both studies were well-

- conducted and met their primary endpoint
- iii. Inclusion of p-values will provide the physician with appropriate information to directly compare the data between the different treatment options enabling them to provide the best treatment option for their patients
 - iv. As presented in the preNDA meeting, Novartis has conducted modeling and simulation for Sandostatin LAR 40 mg and concluded that there would have been no/minimal impact on the trial outcome. We are happy to share this in more detail with you
 - v. Although approved from the beginning (i.e. since 1998) the 40 mg dose is only being used in ^(b)₍₄₎% of cases in the US

2) Safety

- a. We agree to most of the Agency's suggestions including the presentation of adverse reactions regardless of suspectedness and Core phase data for study C2305
- b. We strongly believe that the comparator data is important in understanding the safety of the compounds used in the studies. This presentation is also in accordance with the FDA labeling guidance
- c. These data are critical to enable physicians to make a benefit-risk assessment of available therapeutic options for their patients
- d. With specific reference to hyperglycemia, we strongly believe it is important to inform physicians regarding the mechanism of pasireotide-induced hyperglycemia and ADA guidelines to manage this side effect and to better enable physicians to select appropriate treatment options

I would be happy to further elaborate and discuss these topics with Dr. Guettier and yourself. Alternatively, we would like to schedule a TC with the division early next week to seek alignment on the label.

Regards,
Shanthi.

Shanthi Ganeshan, Ph.D.

VP & US Head, DRA Oncology
Oncology Global Development
Novartis Pharmaceuticals Corporation
Phone: +1 862 7782673
Cell: ^(b)₍₆₎

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/s/

JENNIFER L JOHNSON

12/11/2014

FDA edits to package insert sent via email to applicant on 12/10/14

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, November 26, 2014 5:13 PM
To: Gao, Rose (rose.gao@novartis.com)
Subject: NDA 203255 (Signifor LAR): FDA revisions and comments on PI
Attachments: FDA edits to Signifor LAR PI 26 Nov 2014 tracked changes.doc; FDA edits to Signifor LAR PI 26 Nov 2014 CLEAN.doc

Dear Rose,

Please find attached the Signifor LAR package insert with FDA revisions and comments incorporated.

Both tracked changes and clean versions are included.

We request that you make your changes to the clean version and send back by close of business on **Friday, December 5th**.

Regarding Section 2, we have added a subsection 2.6 which incorporates the IFU contents per 21 CFR 201.57(c)(3)(iv):
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

(iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; and the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.")

Keep in mind that further edits to the patient labeling are anticipated.

Let me know if you have any questions.

Thank you again for your team's extended patience.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

JENNIFER L JOHNSON

11/26/2014

FDA edits to package insert and patient labeling (sent to the sponsor via email on 11/26/14);
concurrence from Jean-Marc Guettier

From: Johnson, Jennifer
To: [Gao_Rose \(rose_gao@novartis.com\)](mailto:rose_gao@novartis.com)
Bcc: Johnson_Jennifer
Subject: NDA 203255 (Signifor LAR): CDRH/OC/DMQ Information Requests
Date: Monday, November 17, 2014 1:55:00 PM

Dear Rose,

The Office of Compliance (OC)/Division of Manufacturing & Quality (DMQ) within the Center for Devices and Radiological Health (CDRH) has completed their review, an evaluation of your compliance with applicable Quality System Requirements for the approvability of NDA 203255, Signifor LAR.

During their review, the following deficiencies were found regarding adequately addressing the requirements per 21 CFR 820:

1. Per the application documentation several firms are involved in the manufacturing of the Signifor LAR finished product. However, your firm did not specify which firm has ultimate responsibility over the overall combination product. Your firm did not describe the organizational structure (i.e., organization structure chart) and explain how it controls all levels of the structure (i.e., agreements). Therefore, the information provided by your firm has inadequately addressed the requirements of 21 CFR 820.20.
2. Your firm provided information covering the activities performed to verify and validate the design of the combination product. However, your firm did not describe its design control system covering requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file. Your firm did not provide the plan used for the design development of the combination product. Your firm did not describe how it implemented the plan to develop the combination product. Therefore, the information provided by your firm has inadequately addressed the requirements of 21 CFR 820.30.
3. Per the application, multiple materials including device constituent components will be supplied by contractors. However, your firm did describe your purchasing control process covering supplier evaluation process, record maintenance of acceptable suppliers, and method to assure that changes made by contractors/suppliers will not affect the final combination product. Your firm did not explain how it applied its purchasing controls to the suppliers/contractors involved in the manufacturing of the combination product or provide evidence of the application (i.e., supplier agreement). Therefore, the information provided by your firm has inadequately addressed the requirements of 21 CFR 820.50.
4. Your firm did not provide any information pertaining to its Corrective and Preventive Action (CAPA) System. The CAPA system should require analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions. Therefore, the information provided by your firm has inadequately addressed the requirements of 21 CFR 820.100.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Please address these deficiencies/information requests both via email and an official amendment submission to the NDA application as soon as possible, and let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

JENNIFER L JOHNSON

11/17/2014

CDRH/OC/DMQ deficiencies/information requests sent via email to sponsor (conveyed to RPM via emailed review on 11/16/14)

From: Johnson, Jennifer
To: "[Gao, Rose](#)"
Bcc: [Johnson, Jennifer](#)
Subject: RE: Novartis NDA 203255 - Signifor LAR - *FDA comments on demo kit IFU*
Date: Wednesday, November 05, 2014 2:26:00 PM
Attachments: [Instructions for Use for demo placebo final.docx](#)

Dear Rose,

We reviewed the IFU for the demonstration kit (attached) and would like to provide the following recommendations:

1. Depending on how the Demo Kit packaged, it may or may not make sense to have the separate Demo IFU. If the Demo Kit packaged in one box with Demo IFU, then it is acceptable to have a separate Demo IFU. If Demo Kit does not contain IFU within a box, then use the regular IFU.
2. Revise the title of "Instructions for Proper Suspension Technique Demonstration Kit" to "Instructions for Use: **Demonstration** Kit" as this IFU is intended to instruct users on how to use the demonstration kit and not solely for proper suspension technique.
3. In Step 1, revise the statement (b) (4) to "Demonstration Kit" since this IFU is intended for the Demonstration Kit (b) (4).

Please let me know if you have any additional questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Phone: (301) 796-2194
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jennifer.johnson@fda.hhs.gov

From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Friday, October 17, 2014 2:50 PM
To: Johnson, Jennifer
Subject: RE: Novartis NDA 203255 - Signifor LAR

Dear Jennifer,

Thank you for your updates! It is very helpful. Our team is looking forward to receiving PI comments next week.

Since IFU for Signifor LAR has been reviewed by the FDA with no further comments, our team would like to submit IFU for **placebo demonstration kit** to the FDA. The basic procedure wording in placebo demo kit IFU is the same as active IFU except few differences (ie. purpose of IFU; not for human use). Please let me know if you have any comments.

Have a great weekend!

Best Regards

Rose Gao
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/s/

JENNIFER L JOHNSON

11/05/2014

DMEPA comments (sent to RPM via email on 11/4/14) re: applicant's proposed demonstration kit IFU



NDA 203255

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Novartis Pharmaceuticals Corporation
Attention: Rose Gao, MS
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gao:

Please refer to your New Drug Application (NDA) dated and received November 15, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Signifor LAR (pasireotide) intramuscular injection, 20 mg, 40 mg, 60 mg.

On August 26, 2014, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **December 15, 2014**.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER L JOHNSON
09/02/2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Follow-up Biopharmaceutics Information Requests
Date: Wednesday, August 27, 2014 11:42:00 AM

Dear Rose,

We have the following biopharmaceutics information requests:

1. *The dissolution acceptance criteria you proposed in your 6/12/14 response to our 5/29/14 information requests are acceptable. Please update and resubmit the specification table and other relevant documents in your NDA.*
2. *In the same response (dated 6/12/14), you confirmed that PK parameters (AUC and Cmax) were based on the actual values,* (b) (4)

[Redacted content]

Please respond as soon as possible.

Let me know if you have any questions – thank you for your help!

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
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/s/

JENNIFER L JOHNSON
08/27/2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Sunday, August 24, 2014 11:11:00 PM

Dear Rose,

Regarding NDA 203255, Signifor LAR, we have the following clinical information requests:

- 1) In clinical trials C2305 and C2402 you present IGF-1 results as “standardized IGF-1”. Was the “standardized IGF-1” normalized to both age and gender?
- 2) Traditionally, IGF-1 levels are expressed either as absolute value or as a standard deviation score (IGF-1 SDS). What is the relationship between a “standardized IGF-1” and IGF-1 SDS (e.g., is there a conversion factor)?
- 3) What is the normal range for “standardized IGF-1” values? For instance, does a “standardized IGF-1” value of 2 represent the upper limit of normal? Is a “standardized IGF-1” value of 2.1 an above-normal value? Is a “standardized IGF-1” value of 1.9 considered within the normal range?

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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/s/

JENNIFER L JOHNSON

08/25/2014

IR from Dragos Roman (clinical TL) sent to applicant on 8/24/14

From: Johnson, Jennifer
To: "[Gao, Rose](#)"
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Further information requests regarding (b) (4) syringe system
Date: Tuesday, August 19, 2014 11:21:00 AM
Attachments: [image001.png](#)

Dear Rose,

Thank you again for providing the requested information regarding the container closure system. We have discussed further internally and have the following comments and requests for clarification.

During previous communications with CDER, you have clarified that the current (b) (4)

However, based on the FDA database, the 2 mL solution "vehicle for powder for suspension for injection", which will be pre-filled in the syringes and proposed for Signifor LAR (pasireotide) intramuscular injection in NDA 203255, (b) (4)

The current vehicle solution has introduced new chemicals which may raise additional device-drug material compatibility issues. In your submission dated June 30, 2014 (in response to our information request sent on June 10, 2014), you state that chemical leachability testing has been conducted. However, the testing information provided in your response is not clear and adequate.

Please address the following issues and provide the revised chemical leachability testing report and the associated risk assessment for the (b) (4) syringe system:

1. Confirm that the chemical leachable studies were performed using the same pre-filled syringes as proposed for Signifor LAR (pasireotide) intramuscular injection in NDA 203255.
2. Clearly identify the list of chemical compounds screened in the leachability testing and justify for the adequacy.
3. Clearly identify the list of chemical compounds detected and specify the concentrations of all leachables/residues per device component (wt/wt). Provide a risk assessment for all identified leachable chemicals based on the target population and a worst case scenario.
4. You state that at higher temperatures, (b) (4)
Provide a risk assessment on the leachable (b) (4) based on the target population and a worst case scenario.
5. The chemical leachable studies were performed under the following storage conditions: 5°C/ambient RH, 25 °C/60% RH, and/or 30 °C/75% RH. Concerns regarding the leachable chemicals at higher temperatures under the worst case conditions (e.g., summer time while the

storage room is not air conditioned), have not been adequately addressed. Please provide chemical leachable and extractable analysis for the worst case conditions. Alternatively, provide your recommended risk mitigation procedure and appropriate caution/warning statement in the labeling.

Please let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Monday, August 18, 2014 8:15 AM
To: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Jennifer,

We'd like to confirm that the container closure system for Signifor LAR diluent (b) (4)
'new' diluent (b) (4)
In fact the (b) (4)

Please find a tabular overview as well in the following:

Container closure components	Signifor LAR diluent (NDA 203255)	(b) (4)
(b) (4) syringe (glass barrel, hub,	✓	

fingergrip, cap)		(b) (4)
Plungerrod	✓	
Front stopper	✓ (b) (4) rubber)	
Plunger stopper	✓ (b) (4) rubber)	

Please let me know if you think we will need a TC at 12 pm today with CDRH reviewer. Looking forward to hearing from you.

Best Regards

Rose Gao
Director Oncology Drug Regulatory Affairs
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 Phone +1 8627786795
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 Fax +1 9737818545
rose.gao@novartis.com
www.novartis.com

From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Friday, August 15, 2014 4:00 PM
To: Gao, Rose
Subject: RE: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Rose,

Just to follow up on my email below, I've scheduled a tentative TC with our team for Monday, August 18th at 12:00 pm EST. I hope that this works for your team, and that you can provide a conference dial-in number and passcode. We can discuss further on Monday morning. Thanks again for your help!

Kind Regards,
 Jennifer

Jennifer Johnson

Regulatory Health Project Manager
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From: Johnson, Jennifer
Sent: Friday, August 15, 2014 1:17 PM
To: Gao, Rose
Subject: RE: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Rose,

Thanks again for sending the information below. However, we are still unclear as to whether the (b) (4) syringe systems for both products (b) (4).

In your response submission on July 14, 2014, you state that the current (b) (4) syringe system proposed for use for Signifor LAR in NDA 203255 contains new device components or has introduced new materials which are not included in the previous (b) (4) syringe system (b) (4) (b) (4)

The subject device has not been 510(k) cleared either. However, when we reviewed what was in NDA 203255 (b) (4) the materials were listed (b) (4) we will need additional biocompatibility testing. Can you please confirm what exactly is the case? If the materials are (b) (4) we should have a teleconference on Monday with your team and reviewers from CDRH to discuss. As a reference, I have attached the relevant components of your submissions (both NDA 203255 (b) (4)) to this email.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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From: Gao, Rose [<mailto:rose.gao@novartis.com>]

Sent: Tuesday, August 12, 2014 9:36 AM
To: Johnson, Jennifer
Subject: RE: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Jennifer,

Please find our responses in green (below) for two syringe questions received yesterday. Please let me know if you have any additional questions. Could you please advise if these responses should be submitted formally through gateway or not. Many thanks!

Has the syringe that you plan on marketing with the drug product been 510(k) cleared? If so, could you please provide us with the 510(k) number?

As indicated in response document 7006364_ANSW_MP_840_4 (NDA 203255/S-016, submitted on 11 July 2014), as the (b) (4) syringe system is considered as a component of a combination product and not a medical device, it is not covered under any 510(k) and has not been cleared by the FDA. The supplier (b) (4) has filed a DMF instead with the CDER.

(b) (4) (b) (4)
(b) (4) If not, what is the 510(k) number for this syringe?

It is confirmed that the (b) (4) syringe system with all its components, i.e.

- (b) (4) syringe (consisting of syringe barrel, hub, fingergrip and cap)
- Front stopper
- Plunger stopper
- Plungerrod

(b) (4)
(b) (4)
(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

Please note:

In 7006364_ANSW_MP_840_4 (NDA 203255/S-016), we had indicated the following under reference of the 'situation prior to approval of new diluent' since (b) (4)

(b) (4)

With the approval of (b) (4) new diluent the (b) (4) syringe system (b) (4)

(b) (4)

(b) (4)

Signifor LAR.

Best Regards

Rose Gao

Director Oncology Drug Regulatory Affairs

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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]

Sent: Monday, August 11, 2014 4:53 PM

To: Gao, Rose

Subject: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Rose,

We have a couple of questions for you regarding the device (pre-filled syringe) being reviewed under NDA 203255, Signifor LAR.

Has the syringe that you plan on marketing with the drug product been 510(k) cleared? If so, could you please provide us with the 510(k) number?

(b) (4)

(b) (4)

If not, what is the 510(k) number for this syringe?

Let me know if you have any questions.

Thanks for your help,

Jennifer

Jennifer Johnson

Regulatory Health Project Manager

Division of Metabolism and Endocrinology Products

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/s/

JENNIFER L JOHNSON

08/19/2014

IR to sponsor from CDRH (Keith Marin and Bifeng Qian) on 8/18/14 following internal meeting

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): FDA edits to package insert
Date: Monday, August 18, 2014 5:10:00 PM
Attachments: [FDA edits to Signifor LAR PI 18 Aug 2014.doc](#)

Dear Rose,

Please find attached the first draft of the Signifor LAR package insert, with FDA edits incorporated. We have made revisions to CMC Sections 3, 11 and 16, and to pharmacology/toxicology Sections 8.1-8.3 and 13.

Edits have been made to the Highlights section as well.

Further edits will be made to the PI as labeling review by other disciplines is completed.

Please review with your team and reply with a response draft, accepting those changes with which you agree and adding any revisions/comments you see fit. (Note: there is no need to send your response via official Gateway submission at this time; email will suffice.)

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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JENNIFER L JOHNSON

08/18/2014

First round of FDA edits to PI sent to sponsor (edits from CMC and nonclinical reviews incorporated into sponsor's latest PI submitted on 2/14/14)

From: Johnson, Jennifer
To: "[Gao, Rose](#)"
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): FDA Requests for Revisions - Carton/Container Labels
Date: Thursday, August 14, 2014 6:21:00 PM

Dear Rose,

Thank you again for sending revised Signifor LAR carton and container labels on July 21st (vial, syringe, carton) and August 7th (tray foil).

We have reviewed the labels, and are requesting the following additional revisions:

A. Container Labels – Vial

1. There is insufficient differentiation between the different strengths. The only difference between the three strengths is the font color of the strength placement, which may be inadequate in preventing selection of the wrong strength error. Thus, provide sufficient differentiation between the three strengths through the use of colors, boxing, or other means for the background to highlight the different strengths.

2. As currently presented,  (b) (4)

B. Container Labels – Syringe

1. As currently presented, the proprietary name "Signifor LAR" in the statement "Diluent for suspension of Signifor LAR" appears more prominent than the word "Diluent". Revise the statement to increase the prominence and readability of the word "Diluent" to reduce the risk of wrong drug error where the diluent is administered instead of the actual drug. For example:

Diluent
for suspension of
Signifor LAR

2. As currently presented, the label for the pre-filled syringe appears more prominent than the drug vial label. Since the diluent amount in the pre-filled syringes is the same for all drug vials regardless of the strength, remove the background color for the syringe label and change the font color to black for the diluent part of the syringe label to make the syringe label less prominent than the drug vial label. The only exception to this recommendation for font color change is to make the statement " PEEL OFF OUTER LAYER AFTER PRODUCT SUSPENSION" more prominent through the use of colors, boxing, or other means to indicate that the drug has been reconstituted. We recommend this to minimize the risk of wrong drug error where the diluent is administered

instead of the actual drug based on our post-marketing experiences.

3. Increase the prominence of the important information on the clear syringe label (bottom half) for Signifor LAR by enhancing the contrast of the font color in comparison with the clear label to improve readability.

4. We note the use of trailing zeroes on the pre-filled syringe labels for the list of ingredients (e.g., sodium CMC 14.0 mg, water for injection, 2.0 mL, etc.). Remove the trailing zeroes for all ingredients (e.g., 14 mg, 2 mL) to avoid a ten-fold misinterpretation.

C. Tray Labeling

1. Add the statement “For single use only” on the principal display panel to minimize the risk of the product components being used multiple times.

2. The tray labeling does not have any differentiation features to facilitate strength selection due to black font on a white background. Add differentiating features to the tray labeling by using colors, boxing, or other means to facilitate strength differentiation and prevent product confusion since our post-marketing experiences indicate that box labeling and tray labeling are frequently separated prior to drug administration.

3. Increase the prominence of the instructions regarding to store the injection kit at room temperature for a minimum of 30 minutes by using a different font color or by boxing the information to highlight the important instructions since 18 participants failed to state intent to wait a minimum of 30 minutes in the human factors study.

D. Carton Labeling – Box Labeling

1. See Section B.4.

2. See Section C.3.

3. Add the statement “Should only be administered by a trained health care professional” on the principal display panel if space permits.

1 Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014; 19(2):1-3.

Please submit revised carton and container labels to me via email, and let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products

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From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Thursday, August 07, 2014 4:47 PM
To: Whitehead, Richard; Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): packaging labeling

Dear Rich and Jennifer,

On July 21, we submitted the updated Signifor LAR packaging labels for vial, syringe and carton of each strength by incorporating recent changes made to other labels (including Sandostatin LAR). I would like to send Tray Foil label of each strength for completeness purpose for continued review by DMEPA and CMC reviewers. Please find attached.

I would like also to give you a heads-up that the updated Demonstration Kit packaging labels will be submitted to you in next 1-2 weeks by email.

As discussed previously, once the FDA reviewers complete their review on updated labeling, we will incorporate all of the revisions at one time to submit to the FDA.

Please let me know if you have any questions.

Best Regards

Rose Gao
Director Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
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From: Stamatis, Demetre
Sent: Monday, July 21, 2014 11:23 AM
To: Jennifer.Johnson@fda.hhs.gov; Gao, Rose
Subject: RE: NDA 203255 (Signifor LAR): Clinical Information Requests

Dear Jennifer,

Per your email below, attached are the revised labels for continued review by DMEPA and CMC

reviewers. Our understanding is that we would then submit these formally after addressing any additional comments from the reviewers.

Please let me know if you have any questions or would like us to proceed differently with the submission of the labels.

Thank you very much,
Demetre

Demetre Stamatis, Pharm.D.
Global Program Regulatory Manager
Drug Regulatory Affairs
Oncology Global Development
Novartis Pharmaceuticals Corporation
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/s/

JENNIFER L JOHNSON

08/15/2014

Email sent to sponsor 8/14/14, requesting revisions to carton/container labels (per DMEPA review dated 3/28/14)

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Friday, August 15, 2014 11:53:00 AM

Dear Rose,

For NDA 203255, Signifor LAR, we have the following clinical information requests:

1. In CSR 2305, Table 14.2-2.13 shows a minimum value of 0.9 µg/L for IGF-1. Does this number imply a non-elevated IGF-1 level? If so, how many patients had IGF-1 levels that were not elevated? Should these patients be considered protocol deviations? And, what criteria allowed the patient(s) to be enrolled into the study?
2. Post transsphenoidal (TSS) surgery for acromegaly, it can often take 3 months for IGF-1 levels to lower and/or reach a steady state level. Table 11-3 in CSR 2305 shows that there may have been some patients who had TSS as soon as 1.6 months prior to enrolling in the trial. How many patients had TSS within 3 months and 6 months of enrolling into this trial?
3. For CSR C2402, Table 11-2 shows that there is a baseline minimum GH value of less than 2.5 µg/L in all three treatment groups as well as low (i.e., not elevated) standardized values of IGF-1 in the range of 0.93 – 1.1. However, the number of protocol deviations shown in Table 10-2 of the CSR does not seem to match the number of non-elevated values. For example, it appears that there is at least one patient with a GH value of 0.98 and one patient with an IGF-1 value of 0.93 (Table 11-2), which would imply 2 protocol deviations. If these values occurred in the same patient, please explain why the patient was included. Overall, please clarify the number of patients with GH levels < 2.5 µg/L and those with non-elevated IGF-1 levels and how these numbers correlate to the number of protocol deviations.

Please let me know if you have any questions.

Kind Regards,
Jennifer

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/s/

JENNIFER L JOHNSON

08/15/2014

Information requests received from clinical reviewer Smita Abraham on 8/15/14

From: Johnson, Jennifer
To: "Gao, Rose"
Bcc: Johnson, Jennifer
Subject: RE: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance
Date: Friday, August 15, 2014 1:16:00 PM
Attachments: [cmc-responses-fda-device 7-14-14.pdf](#)
(b) (4)
[NDA 203255 container-closure-system.pdf](#)
[image001.png](#)

Dear Rose,

Thanks again for sending the information below. However, we are still unclear as to whether the (b) (4) syringe systems for both products (b) (4).

In your response submission on July 14, 2014, you state that the current (b) (4) syringe system proposed for use for Signifor LAR in NDA 203255 contains new device components or has introduced new materials which are not included in the previous (b) (4) syringe system (b) (4)

(b) (4) The subject device has not been 510(k) cleared either. However, when we reviewed what was in NDA 203255 (b) (4) the materials were listed (b) (4) we will need additional biocompatibility testing. Can you please confirm what exactly is the case? If the materials are (b) (4) we should have a teleconference on Monday with your team and reviewers from CDRH to discuss. As a reference, I have attached the relevant components of your submissions (both NDA 203255 (b) (4)) to this email.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Tuesday, August 12, 2014 9:36 AM
To: Johnson, Jennifer
Subject: RE: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Jennifer,

Please find our responses in green (below) for two syringe questions received yesterday. Please let me know if you have any additional questions. Could you please advise if these responses should be submitted formally through gateway or not. Many thanks!

Has the syringe that you plan on marketing with the drug product been 510(k) cleared? If so, could you please provide us with the 510(k) number?

As indicated in response document 7006364_ANSW_MP_840_4 (NDA 203255/S-016, submitted on 11 July 2014), as the (b) (4) syringe system is considered as a component of a combination product and not a medical device, it is not covered under any 510(k) and has not been cleared by the FDA. The supplier (b) (4) has filed a DMF instead with the CDER.

(b) (4) (b) (4)
If not, what is the 510(k) number for this syringe?

It is confirmed that the (b) (4) syringe system with all its components, i.e.

- (b) (4) syringe (consisting of syringe barrel, hub, fingergrip and cap)
- Front stopper
- Plunger stopper
- Plungerrod

(b) (4)

(b) (4)

(b) (4)

- (b) (4) (b) (4)
- (b) (4)
- (b) (4)

Please note:

In 7006364_ANSW_MP_840_4 (NDA 203255/S-016), we had indicated the following under reference of the 'situation prior to approval of new diluent' (b) (4)

(b) (4)

(b) (4) (b) (4)

With the approval of (b) (4) new diluent the (b) (4) syringe system (b) (4) (b) (4) Signifor LAR.

Best Regards

Rose Gao
Director Oncology Drug Regulatory Affairs
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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Monday, August 11, 2014 4:53 PM
To: Gao, Rose
Subject: NDA 203255 (Signifor LAR): Question regarding device 510(k) clearance

Dear Rose,

We have a couple of questions for you regarding the device (pre-filled syringe) being reviewed under NDA 203255, Signifor LAR.

Has the syringe that you plan on marketing with the drug product been 510(k) cleared? If so, could you please provide us with the 510(k) number?

[REDACTED] (b) (4) [REDACTED] (b) (4)
[REDACTED] ? If not, what is the 510(k) number for this syringe?

Let me know if you have any questions.

Thanks for your help,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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/s/

JENNIFER L JOHNSON

08/15/2014

IR from CDRH (Keith Marin) on 8/15/14, follow-up to sponsor's 8/12/14 response to 8/11/14 IR

From: Johnson, Jennifer
To: demetre.stamatis@novartis.com
Cc: [Gao, Rose \(rose.gao@novartis.com\)](mailto:Gao, Rose (rose.gao@novartis.com))
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Monday, July 21, 2014 5:24:00 PM

Dear Demetre,

Regarding NDA 203255 (Signifor LAR), we have the following clinical information requests:

- 1) Please provide the exact amounts of the research grants received by [REDACTED] (b) (6) [REDACTED] (Table 4-1, entitled "Investigator disclosures of financial arrangements", located on page 3 of the financial disclosure certification found in module 1, section 1.3.4 of the original NDA submission).
- 2) Regarding adverse events by gender in Studies C2305 and C2402, provide a summary of the CORE phase results using the following table shell as a guide:

Table.

	Pasireotide LAR		Octreotide LAR	
Primary SOC	All grades n (%)	G3/G4	All grades n (%)	G3/G4
	Male	Male	Male	Male
	Female	Female	Female	Female

- 3) For Studies C2305 and C2402, provide a similar table to that in #2 for adverse event categorization by race and age.
- 4) How many responders in both the pasireotide and active control arms in Studies C2305 and C2402 were taking estrogen? Please provide the patient IDs of all who were taking estrogen.
- 5) How many over-responders in both the pasireotide and active control arms in Studies C2305 and C2402 were taking estrogen?

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
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/s/

JENNIFER L JOHNSON

07/21/2014

IRs received from clinical reviewer Smita Abraham via email on 7/21/14

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Cc: demetre.stamatis@novartis.com
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Additional Clinical Information Requests
Date: Thursday, July 17, 2014 1:07:00 PM

Dear Rose,

We have a few additional clinical information requests for NDA 203255, Signifor LAR:

1. Please provide the rates of anemia in the up to crossover phase in Study C2305. Also provide the definition of anemia used to define this adverse event in both Studies C2305 and C2402.
2. For patient C2402-0601-00001, the narrative reports that the patient “underwent an abortion”. Was this a spontaneous abortion or a medical procedure?
3. Regarding our question #9 (included in our clinical information requests sent to you on Monday, July 14th and repeated below), the patient ID is **C2402-0440-00008**.

On page 671 of Appendix 2 in the Clinical 120 Day Safety Update submission, a narrative is provided for a patient who became pregnant while on pasireotide LAR. However, the dates of treatment in relation to the pregnancy are confusing. Please confirm that this patient was taking pasireotide LAR (and what dose) during the CORE and extension phase of Study C2402 and provide the dates accordingly. At present, it seems that the patient took the last dose of pasireotide LAR in July 2012 and became pregnant almost 1 year later after June 2013.

Let me know if you have any questions.

Kind Regards,
Jennifer

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/s/

JENNIFER L JOHNSON

07/17/2014

Additional information requests from clinical reviewer Smita Abraham via emails on 7/16 and 7/17

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Monday, July 14, 2014 5:52:00 PM

Dear Rose,

For NDA 203255 (Signifor LAR) currently under review, we have the following clinical information requests:

- 1) Regarding Study C2305, section 12.3.3.1 (page 202, CSR): the text that appears on this page along with Table 12-16 indicates that 9 patients in the octreotide LAR group discontinued study drug. However, we are finding it difficult to replicate this number from the datasets. We count 7 discontinuations with 6 patients who discontinued in the core phase and 1 patient who discontinued in the extension phase. Please clarify, and in your response, provide the patient IDs of the 9 patients who discontinued due to adverse events in the octreotide LAR group.
- 2) In Study C2305, patient 0912-00012 experienced the SAEs of adrenal insufficiency and cholelithiasis. There is a narrative provided for this patient. However, these SAEs do not appear to be represented in Table 14.3.1-3.1.3 of the C2305 CSR nor are they counted as SAEs in Tables 12-4, 12-5 or any other text/table that sums the number of SAEs. This patient was randomized to octreotide LAR in the core phase and then crossed over to pasireotide LAR. The SAEs should be listed in the octreotide LAR group; however, they do not appear to be listed in serious adverse event listings for either group.
- 3) The withdrawal criteria related to QTc prolongation listed on page 95 of the Study C2305 CSR are many more than what is stated for QTc prolongation in the Study C2402 withdrawal criteria on page 59 of the C2402 CSR. Also, in C2305, a QTc interval > 470 ms is listed as a discontinuation criterion versus a QTc interval of > 480 ms in C2402. Similarly, onset of angina pectoris is a criterion for C2402 and not for C2305. Please explain the differences.
- 4) In your May 30, 2014, response to our clinical information request received on May 16, 2014, you provide detailed laboratory results for patient C2305_0506_00006. The results show several elevated glucose results > 200 mg/dl. The glucose abnormality withdrawal criterion states: "Uncontrolled diabetes mellitus, defined as blood glucose values consistently in excess of 200 mg/dl or HbA1c value \geq 8 % in spite of continuous, appropriate therapeutic intervention(s)". Why was this patient not discontinued? Are there other patients in either C2305 or C2402 who had situations like this, where they appear to have met withdrawal criteria but were not withdrawn? Please explain.
- 5) Regarding Study C2305, page 161 of the CSR: did any participating sites outside the U.S. conduct OGTTs? If so, how many patients from these sites had an OGTT performed at any point (i.e., baseline, Month 12, extension) in the study? Of the 28 patients in the

pasireotide LAR group and the 44 patients in the octreotide LAR group who had an OGTT performed at Month 12, how many met the primary efficacy endpoint? Was there agreement between those who suppressed GH to < 1 ug/L on the OGTT and those who met the primary efficacy endpoint? Similarly, was there agreement between those who suppressed GH to < 1 ug/L on the OGTT and those who normalized IGF-1 (regardless of GH level)?

- a) For the Study C2402 data, provide a table with OGTT results that is similar to Table 11-17 (page 161) in Study C2305 and also provide the number of patients who had an OGTT at Visit 1. Please answer the questions included in #5 for the C2402 study as well.
- 6) Regarding Study C2305, Table 10-4, of the CSR: was any patient enrolled that did not have a mean 5 point GH level or an OGTT GH nadir > 1ug/L; i.e., did every patient have at least one baseline GH assessment?
- 7) As is provided for the patients in Study C2402, please provide the following information for the patients in Study C2305:
 - a) Proportion of patients achieving GH levels < 1.0 µg/L and normal sex- and age-adjusted IGF-1 at 6 and 12 months.
 - b) Proportion of patients achieving GH levels < 1.0 µg/L at 6 and 12 months.
- 8) On page 88 of the Clinical Safety Update Appendix 3, there is a safety update to previously submitted narratives for patient C2305-0206-00004 entitled: “Discontinuation due to AE (type 2 diabetes mellitus), elevated liver function tests (blood bilirubin increased)”. However, we cannot find the previously submitted narrative in the Study C2305 CSR. Also, within the narrative there is no mention of type 2 diabetes mellitus or discontinuation of the study drug. Please clarify.
- 9) On page 671 of Appendix 2 in the Clinical 120 Day Safety Update submission, a narrative is provided for a patient who became pregnant while on pasireotide LAR. However, the dates of treatment in relation to the pregnancy are confusing. Please confirm that this patient was taking pasireotide LAR (and what dose) during the CORE and extension phase of Study C2402 and provide the dates accordingly. At present, it seems that the patient took the last dose of pasireotide LAR in July 2012 and became pregnant almost 1 year later after June 2013.
- 10) Regarding Studies C2305 and C2402, in the safety section entitled, “Adverse events requiring significant additional therapy”, what defines “significant”?
- 11) Regarding Study C2305, pages 220-221, Table 12-27: please provide data for “Grade 2” for “Sodium (hypo)”, which is missing from the clinical study report.

Let me know if you have any questions or concerns.

Thank you in advance for your help.

Kind Regards,
Jennifer

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/s/

JENNIFER L JOHNSON

07/14/2014

Email to sponsor - clinical information requests received from clinical reviewer Smita Abraham on 7/14/14

From: Johnson, Jennifer
To: ["Gao, Rose"](#)
Bcc: [Johnson, Jennifer](#)
Subject: RE: NDA 203255 (Signifor LAR): Quality/Device Information Requests - *Submission timeline + additional requests*
Date: Monday, June 30, 2014 2:41:00 PM

Dear Rose,

Thank you again for your patience in awaiting a response. I have discussed with my device reviewers your proposal to submit pyrogenicity and bacterial endotoxin test results during the week of August 4th. While we understand that the timeline you suggested is already an accelerated one for your team, if you can submit it any earlier that would be more desirable, as we have an internal deadline of August 11th for completion of primary reviews.

Also, we have additional information requests related to the device and biocompatibility – see below:

1. Please clarify if the (b) (4) syringe system has been previously cleared by the FDA. If yes, provide the 510(k) number. If not, address the following concerns regarding the biocompatibility of the device as review of the Drug Master File indicates that (b) (4) is not providing the final finished device:

- a) For the device components that will contact drug/fluid path or blood path, provide complete biocompatibility study reports of the following based on the nature, degree, and duration of exposure, using the final finished subject device:
 - *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for in vitro cytotoxicity;
 - Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
 - Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;
 - Acute systemic toxicity testing based on ISO 10993 Biological evaluation of medical device, Part 11 Tests for systemic toxicity;
 - Haemocompatibility testing based on ISO 10993 Biological evaluation of medical devices, Part 4 Selection of tests for interactions with blood.
- b) For the device components that have only limited skin contact, provide the following biocompatibility study reports:
 - *In vitro* cytotoxicity testing based on ISO 10993 Biological evaluation of medical devices, Part 5 Test for in vitro cytotoxicity;
 - Irritation testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization;

- **Delayed hypersensitivity testing based on ISO 10993 Biological evaluation of medical devices, Part 10 Tests for irritation and skin sensitization.**

- 2. You have not provided any testing for evaluation of particulate matters on the device. Particulates that may be present on medical devices pose potential health risks to patients when introduced into drug delivery pathway and/or blood path. Please provide a particulate matter assessment based on USP <788> Particulate Matter in Injections as review of the drug master file indicates that (b) (4) is not providing the final finished device.**

We are requesting responses as soon as you can provide them. Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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From: Gao, Rose [mailto:rose.gao@novartis.com]
Sent: Wednesday, June 25, 2014 12:29 PM
To: Johnson, Jennifer
Subject: RE: NDA 203255 (Signifor LAR): Quality/Device Information Requests

Dear Jennifer,

To follow up with the voice mail, I am sending this email.

We are in a process of finalization of our response document for the requests received on 10-June-2014 (below). The response submission is targeted for June 30 (next Monday). Our CMC team has a question on Q2. We will provide available data and justification in the response to fulfill FDA's recommendation, in addition, NVS would like to commit to submit results of pyrogenicity (the rabbit pyrogen test) and bacterial endotoxins tests at Aug 4th week. In the context of the action date of 15-Sept-2014, I hope Aug 4th week is acceptable to the FDA. Please let me know. Thank you in advance!

Best Regards

Rose Gao
Director Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza

Building 315, 4th Floor
East Hanover, NJ 07936-1080
Phone +1 8627786795
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Fax +1 9737818545
rose.gao@novartis.com
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From: Johnson, Jennifer [<mailto:Jennifer.Johnson@fda.hhs.gov>]
Sent: Tuesday, June 10, 2014 6:01 PM
To: Gao, Rose
Subject: NDA 203255 (Signifor LAR): Quality/Device Information Requests

Dear Rose,

We have the following quality/device information requests for NDA 203255, Signifor LAR:

1. FDA believes that during the conditions of use, leachables from the (b) (4) syringe system may interact with the pre-filled Signifor LAR (pasireotide) and change the safety, potency, and stability of the drug delivered to the patient. To support the drug-device material compatibility, please provide a quantitative and qualitative estimate of the leachables and other residues originating from the syringe. We recommend that you follow the FDA-recognized standard **ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference Materials for preparation of the test samples**. For analysis of leachable and extractable residues and establishing allowable limits, you may consult with **ISO 10993 Biological evaluation of medical devices Part 17: Methods for the establishment of allowable limits for leachable substances, 2002; and Part 18: Chemical characterization of materials, 2005**. Please specify the concentrations of all leachables/residues per device component (wt/wt).
2. As there is a potential for material and bacterial-related pyrogens to be transferred to the patient through fluid during the use of the subject device, FDA believes that material and bacterial-related pyrogen testing would be necessary. Please follow the **FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers (June 2012)**, and provide complete study reports for pyrogenicity using neat test extracts of the final finished, sterilized subject device:
 - a) Material mediated pyrogenicity study (the rabbit pyrogen test), based on **ISO 10993 Biological evaluation of medical device - Part 11: Tests for systemic toxicity**.
 - b) Bacterial endotoxin test (Limulus Amebocyte Lysate test, the amounts of endotoxin expressed as endotoxin units per milliliter, EU/mL), based on

ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing.

We respectfully request responses by the end of June.
Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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JENNIFER L JOHNSON

07/01/2014

CDRH additional device/biocompatibility information requests received from Keith Marin and sent to the applicant on 6/30/14

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Quality/Device Information Requests
Date: Tuesday, June 10, 2014 6:00:00 PM

Dear Rose,

We have the following quality/device information requests for NDA 203255, Signifor LAR:

1. FDA believes that during the conditions of use, leachables from the (b) (4) syringe system may interact with the pre-filled Signifor LAR (pasireotide) and change the safety, potency, and stability of the drug delivered to the patient. To support the drug-device material compatibility, please provide a quantitative and qualitative estimate of the leachables and other residues originating from the syringe. We recommend that you follow the FDA-recognized standard **ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference Materials for preparation of the test samples**. For analysis of leachable and extractable residues and establishing allowable limits, you may consult with **ISO 10993 Biological evaluation of medical devices Part 17: Methods for the establishment of allowable limits for leachable substances, 2002; and Part 18: Chemical characterization of materials, 2005**. Please specify the concentrations of all leachables/residues per device component (wt/wt).

2. As there is a potential for material and bacterial-related pyrogens to be transferred to the patient through fluid during the use of the subject device, FDA believes that material and bacterial-related pyrogen testing would be necessary. Please follow the **FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers (June 2012)**, and provide complete study reports for pyrogenicity using neat test extracts of the final finished, sterilized subject device:
 - a) Material mediated pyrogenicity study (the rabbit pyrogen test), based on **ISO 10993 Biological evaluation of medical device - Part 11: Tests for systemic toxicity**.
 - b) Bacterial endotoxin test (Limulus Amebocyte Lysate test, the amounts of endotoxin expressed as endotoxin units per milliliter, EU/mL), based on ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing.

We respectfully request responses by the end of June.
Please let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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JENNIFER L JOHNSON

06/11/2014

Device-related information requests received from CDRH reviewer/TL Keith Marin on June 5, 2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Biopharmaceutics Information Requests
Date: Thursday, May 29, 2014 4:48:00 PM
Attachments: [Filing Review Issues Identified NDA 203255.pdf](#)

Dear Rose,

Regarding NDA 203255 (Signifor LAR), we have reviewed your responses submitted on February 14, 2014, to the Chemistry/Biopharmaceutics information requests included in the attached 74-day filing letter dated January 28, 2014.

We require further information in order to complete our review:

1. As stated in the 74-day letter,  (b) (4) . Based on the data provided, the following *in vitro* drug release acceptance criteria are recommended. Please provide concurrence and update your NDA specification table.

 (b) (4)

2.  (b) (4)

Please provide responses by **June 12, 2014**.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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JENNIFER L JOHNSON

05/29/2014

Biopharmaceutics IR from reviewer John Duan (TL concurrence by Tapash Ghosh)

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Tuesday, May 27, 2014 4:00:00 PM

Dear Rose,

For NDA 203255 (Signifor LAR), we have the following clinical information requests and related questions:

1. In C2305, are the patients (n=30) with notably low pulse rate (indicating pulse \leq 50bpm with decrease in baseline of \geq 15 bpm) described in Table 14.3-3.1.1 (page 3821 of CSR) a different population than those with sinus bradycardia and bradycardia described in Tables 12-7 (page 189) and 12-20 (page 207; source data 14.3.1-5.1.3 page 3844)? Are the differences in rates related to the Core vs. Extension phase? Are sinus bradycardia and bradycardia preferred terms for the same entity? There are 12 patients with "sinus bradycardia" in Table 12-7 and Table 14.3.1-5.1.3 in the pasireotide LAR group. There are 4 patients with "bradycardia" in Table 14.3.1-5.1.3, but, who do not appear in Table 12-7.
2. In the clinical safety update report, patient C2402-0273-00002 experienced sudden death. The narrative has been reviewed. Can you provide any other data regarding signs and symptoms, laboratory or ECG abnormalities, unusual complaints by the patient etc., from within the last few weeks or months of the patient's death?

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

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JENNIFER L JOHNSON
05/28/2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Friday, May 16, 2014 5:46:00 PM

Dear Rose,

We have the following clinical information requests for NDA 203255, Signifor LAR:

Reference Clinical Study Report C2305:

1. In Table 12-25 (page 217), newly occurring or worsening CTC hematological abnormalities are reported. Please explain why the Total N for "Prothrombin time (INR)" is 55 rather than 178 (or something close to it) as the protocol implies that this parameter was measured in all patients.

Regarding your submission dated April 11, 2014, in response to FDA information request dated March 17, 2014:

1. In Table 2-5 on page 24 (re: C2305), reported in the range, are high hemoglobin values of 205.0, 194.0, 171 g/L at baseline, month 6 and month 12 respectively. Similarly, in Table 2-6 for C2402, reported in the range are high hemoglobin values of 210, 169 and 160 g/L. Please comment and explain such extreme values.
2. In Table 2-9 on page 34 (re: C2305), reported in the range, is a high value of Lipase at 1320 U/L and a high value of Triglycerides of 10.1 mmol/L. Please comment and explain such extreme values.
3. Also in Table 2-9 on page 34 (re: C2305), the high end creatinine values reported are higher in the pasireotide LAR vs. octreotide LAR group. On page 38, Table 2-11 shows that there is a slightly higher number of patients with creatinine levels above the upper limit of normal in the pasireotide LAR vs. octreotide LAR group. Likewise, looking back at the NDA 200677 application, Table 12-9 of the Clinical Study Report shows that approximately 24% patients in both the pasireotide 600 and 900 mcg groups shifted from a creatinine CTC level grade 0 at baseline to worst post-baseline value of grade 1. Please comment on this possible trend of increased creatinine levels over time in patients on pasireotide.
4. On page 33, section 2.8, you provide summary statistics and percentage of patients above and below the limits of normal for biochemistry parameters. Using the same format and timepoints, please provide this information for the electrolytes reported in Table 12-27 (page 220) of Clinical Study Report C2305. Also provide this information for C2402. In addition, in C2305, we noticed that there is a slightly increased rate of hypercalcemia and hyponatremia in the pasireotide LAR vs. octreotide LAR group. Please comment.

Regarding your submission dated April 1, 2014, in response to FDA information request dated March 17, 2014:

5. On pages 3-5, you provide a response to our question #13 regarding discrepancies in Table 5-16 and Table 2-1. For further insight into hepatic safety, please fill in the data for the following table:

Categorical LFT Outliers	Pasireotide LAR N=178	Octreotide LAR N=180
ULN < ALT ≤ 3x ULN		
ULN < AST ≤ 3x ULN		
ULN < AST and ALT ≤ 3x ULN		
ALT > 3x ULN		
AST > 3x ULN		
ALT and AST > 3x ULN		
ALT > 5x ULN		
AST > 5x ULN		
ALT and AST > 5x ULN		
ALT > 10x ULN		
AST > 10x ULN		
ALT and AST > 10x ULN		
TB > ULN and < 2x ULN		
TB ≥ 2x ULN		

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
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JENNIFER L JOHNSON

05/16/2014

Follow up information requests from clinical reviewer Smita Abraham (concurrence from clinical team leader Dragos Roman) on 5/15/14

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Request
Date: Monday, May 12, 2014 8:22:00 PM

Dear Rose,

For NDA 203255 (Signifor LAR) currently under review, we have the following clinical information request:

Please provide the hematology and biochemistry shift tables (similar to tables 12-25, 12-26 and 12-27 in Clinical Study Report C2305), representing only the CORE phase.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
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JENNIFER L JOHNSON
05/12/2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Follow-up Clinical Information Requests
Date: Wednesday, April 23, 2014 3:59:00 PM

Dear Rose,

We have the following clinical information requests for NDA 203255 (Signifor LAR):

1. In your April 11, 2014, response to FDA clinical information requests (pages 14-15), tables displaying the summary of anti-diabetic medications by visit and treatment are provided for the CORE phases of Studies C2305 and C2402. However, in Table 2-3, rows for DPP-4 inhibitors and thiazolidenediones are missing. In Table 2-4, rows for glinides and thiazolidenediones are missing. Also, in your e-mail clarification to FDA on March 19, 2014, you asked to include GLP-1 agonist usage. However, this medication is not represented in the tables either. Please provide this information.
2. In your April 11, 2014, response to FDA clinical information requests (pages 8 and 11), you provide data for completers regarding the number of patients on anti-diabetic treatment at each time point for the duration of the CORE phase for Studies C2305 and C2402, respectively. Please also provide this information for the intention-to-treat population for both C2305 and C2402 as well.
3. In your April 11, 2014, response to FDA clinical information request (page 16-17), you provided Figures 2-1 to 2-4 displaying diabetic status over time in Study C2305 for the intention-to-treat population as well as the completers population. Please provide similar figures representing the Study C2402 intention-to-treat and completers populations.
4. Please provide summary statistics for fasting plasma glucose and treatment by baseline diabetic status for Study C2402. Please do the same for HbA1c. These data should be in a similar format as Table 14.3-2.36 and 14.3-2.37 on pages 3318-3322 of the Study C2402 CSR.
5. On page 185 of the CSR for C2305, it is stated that "...start of insulin was reported in 17/176 patients (9.7%) in the pasireotide group...". In your response to FDA clinical information requests (page 15) received on April 11, 2014, Table 2-3 shows that only 3 patients were on insulin at month 12. While part of the discrepancy may be due to the fact that Table 2-3 reflects CORE data and much of the CSR represents up to crossover safety data, please account for the different numbers. For example, did several of the patients who started insulin end up discontinuing the study?
6. What defined a "clinically significant event"? Specifically, in Study C2402, some of the narratives (clinically significant event section) describing hyperglycemia seem to describe events equal to or worse in severity than those presented in the SAE section (page 3789 C2402 CSR).

7. Please provide reference ranges for the hematologic and biochemical parameters listed in our information requests dated March 17, 2014 (requests 6, 7 and 8). Please also provide the mean \pm SD for baseline, Month 6 and Month 12 (C2305) and baseline and Month 3 and Month 6 (C2402) for bicarbonate. Similarly, please provide the percent above and below limits of normal for bicarbonate at the time points requested in #7 of the FDA information requests dated March 17, 2014, for C2305 and C2402.
8. Please provide summary statistics for vital signs at baseline, Months 3, 6, 9 and 12 for C2305 and baseline, Months 3 and 6 for C2402.
9. Were vital signs measured in a seated or supine position, or both?
10. Regarding vital signs in both studies, what range was defined as normal for systolic and diastolic blood pressure? Pulse? Do the notably abnormal vital signs reported in Table 14.3-3.1.1 for Study C2305 represent the worst post-baseline value?

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
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/s/

JENNIFER L JOHNSON

04/23/2014

Follow-up information requests from clinical reviewer Smita Abraham (concurrence from TL Dragos Roman) on 4/22/14

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Additional Clinical Information Requests Regarding Datasets
Date: Tuesday, March 25, 2014 1:51:00 PM

Dear Rose,

We have the following clinical information requests for NDA 203255, Signifor LAR (pasireotide), regarding the datasets for Studies C2305 and C2402:

Study C2305:

1. Dataset AAEV - in column VISNAM1A – please further define SUMMARY CORE and SUMMARY EXTN.
2. In many of the C2305 data tables you provided (example: Table 14.3.1-5.1.4), there is a time period termed: “up to crossover and prior to month 26”. Which column in the AAEV dataset identifies this time period?
3. Within the Clinical Study Report (CSR) for C2305, the time period “up to crossover” is described. Is this the same as “up to crossover and prior to month 26” as seen in the data tables?

Study C2402:

1. In dataset AAEV, why are there no case IDs in column SAEIDN1A? This column should indicate the case IDs for those patients that experienced an SAE, correct?
2. For dataset AAEV, please further define “0=not crossed and 1= crossed” in the column, AEVSER1C. Does this column identify which patients experienced a serious adverse event?
3. Patient IDs 0151_00014 and 0223_00005 show as having discontinued drug according to column ACNTAK3N. However, it appears that the AE start date occurred several months after the study drug was discontinued. Please explain.
4. In the dataset AAEV, which column should I use to separate out patients who had AEs in the CORE versus the extension?
5. There is an SAE narrative for C2402-0344-00005 for the SAE hypertension but this is not reflected in table 14.3.1-2.1 on pages 3590-3592 of Clinical Study Report CSOM 2402. Also, Table 12-2 on page 110 of the CSR shows a total of 8 SAEs and there are nine narratives provided. Please explain.
6. Explain why Patients 0301_00002 and 0344_00004 are considered as having SAEs as the narratives do not indicate death, life threatening event, hospitalization or persistent or significant disability/incapacity.
7. The premature withdrawal criteria listed on page 59 of the CSR C2402 show that blood glucose values in excess of 240 mg/dl or HbA1c of $\geq 10\%$ would qualify a patient to be withdrawn. This is different than the blood glucose (200 mg/dL) and HbA1c (8%) premature withdrawal criteria used in C2305 (page 96 of CSR C2305). Please explain.
8. There are four narratives (pages 3785-3788 of CSR 2402) provided for patients who discontinued pasireotide LAR 40 mg or 60 mg. Including the narrative of the patient who had an SAE of colon cancer, this totals five. However, in table 12-8 on page 115 of the CSR, there are seven patients who discontinued pasireotide LAR. Although one of those seven

discontinued in the extension, please provide the additional two narratives.

Let me know if you have any questions or concerns.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
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/s/

JENNIFER L JOHNSON

03/25/2014

Clinical information requests from clinical reviewer Smita Abraham (concurrence from Dragos Roman, clinical team leader) on 3/24/14

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Information Requests
Date: Monday, March 17, 2014 5:51:00 PM
Attachments: [Clinical Information Requests Signifor LAR.doc](#)

Dear Rose,

For NDA 203255 (Signifor LAR) currently under review, we have the following clinical information requests (see attached document). While we would appreciate responses as soon as your team can provide them, we do not have a defined due date for submission and responses may be provided in piecemeal if that is more feasible for you.

Let me know if you have any questions or concerns – thanks in advance for your help.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

Clinical Information Requests for Signifor LAR (pasireotide), NDA 203255:

- Using the table shell provided, please create the following table for Studies CSOM2305 and CSOM2402 (separate table for each pivotal study); for Study CSOM2402, represent the visits within the six-month course of the study.

Table

Parameter	Visit	Baseline	Mos 0.5	Mos 1	Mos 1.5	Mos 2	Mos 3	Mos 4	Mos 5	Mos 6	Mos 7	Mos 8	Mos 9	Mos 12
Mean FPG (mg/dl) Pasi Octreo														
M % change FPG from baseline Pasi Octreo														
Mean HbA1c (%) Pasi Octreo														
Mean % change in HbA1c from baseline Pasi Octreo														
N (%) on anti-diabetic meds at each time point and for duration of core phase* Pasi Octreo														

FPS, fasting plasma glucose; Pasi, pasireotide LAR; Octreo, octreotide LAR; mos, month; abnl, abnormal

*N (%) at each time point = # patients on anti-diabetic meds/ # patients on trial at the respective time point.

- Using Table 3.1-53 in the SCS Appendix 1 (page 1197) as a reference, provide the shift in the maximum number of anti-diabetic medication use from baseline to 6 and 12 months by baseline diabetic status for Study CSOM2305; for Study CSOM2402, please do the same, representing the visits within the 6-month course of the study.
- Using the table shell below, provide the number (percent) of patients using each class of anti-diabetic medication at baseline, 6, and 12 months for Study CSOM2305; for Study CSOM2402, do the same, representing the visits within the 6-month course of the study.

Visit ATC class Preferred term*	Baseline Pasi	Mos 6 Pasi	Mos 12 Pasi	Baseline Octreo	Mos 6 Octreo	Mos 12 Octreo
Alpha glucosidase inhibitors alone						
Biguanides alone						
Combination drugs						
DPP-4 inhibitors alone						
Insulins alone						
Sulfonamides alone						
Glinides alone						
Thiazolidenediones alone						

*include totals for class of drug; number per individual drug within the class is not needed
Pasi, pasireotide LAR; Octreo, octreotide LAR; Mos, month

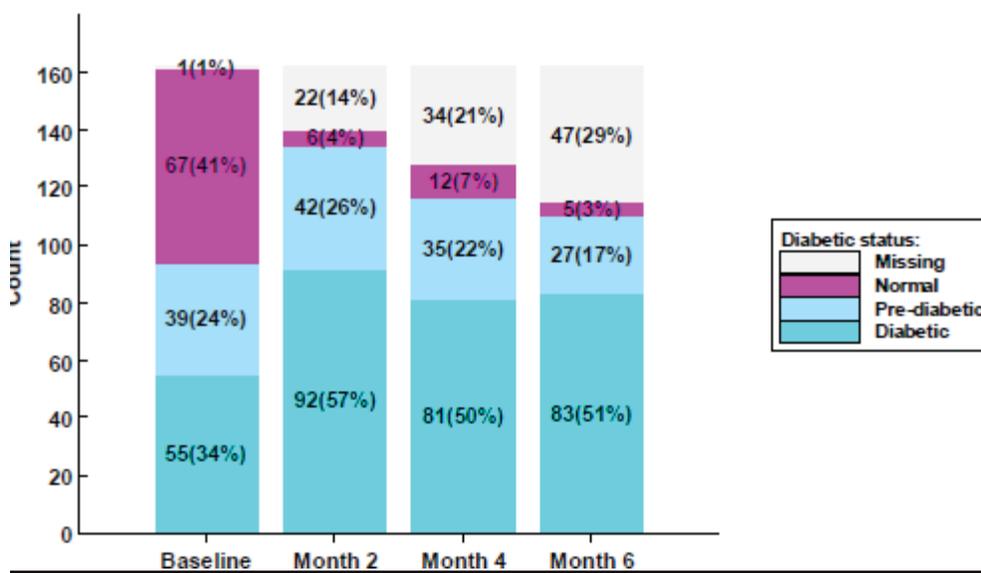
- Please create the following bar graph representing changes in pre-diabetes and diabetes status with the appropriate data for the intention to treat population in Study CSOM2305 including baseline, Month 3, Month 6, Month 9 and Month 12 data. One graph should represent those randomized to pasireotide LAR and a second graph should represent these data in those randomized to octreotide LAR.

Also create this type of graph for:

- patients randomized to pasireotide LAR who completed the CORE phase of the study, and
- patients randomized to octreotide LAR who completed the core phase of the study.

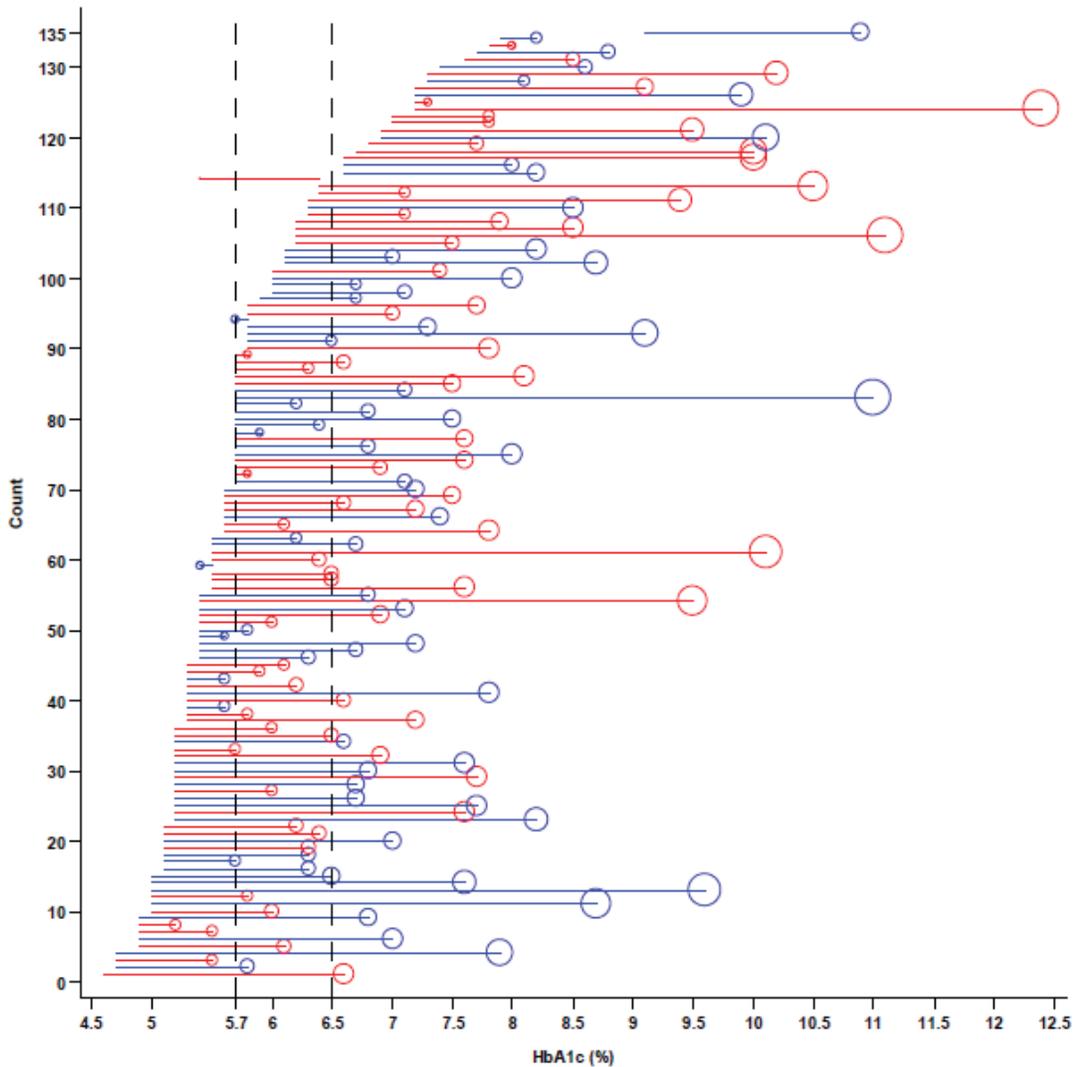
This example is from the pasireotide review for the Cushing's indication (NDA 200677).

Figure 12: Changes in pre-diabetes and diabetes status



5. Provide individual changes in HbA1c from baseline to Month 12 (or last value) in patients on pasireotide LAR and octreotide LAR in the intention-to-treat population in Study CSOM2305 in graph format using the following figure as an example. See example below for Request #5; this figure is from the pasireotide review for the Cushing's indication (NDA 200677):

Figure 11: Individual changes in HbA1c from baseline to Month 6



Sorting is by start value
(smallest sort value at bottom)

Treatment at start:

	Pasireotide 900µg bid
	Pasireotide 600µg bid
○	End (sized to value of HbA1c change)

6. Using the shell below, insert the mean \pm SD (range) for each time point requested for each treatment group for Studies CSOM2305 and 2402.

Table.

Parameter \ Visit	Baseline	Mos 6	Mos 12
WBC (total) Pasi Octreo			
Absolute neutrophils (Seg. + Bands) Pasi Octreo			
Absolute lymphocytes Pasi Octreo			
Hemoglobin Pasi Octreo			
Platelets Pasi Octreo			
Activated partial thromboplastin time Pasi Octreo			
Prothrombin Time (INR) Pasi Otreo			

Pasi, pasireotide LAR; Octreo, Ocreotide LAR; Mos, month

7. Using the table shell below, provide the percent above and below limits of normal for each variable at the given time points for each treatment group for Studies CSOM2305 and 2402.

Table 7. N (%) above and below limits of normal for hematological parameters, by treatment group, during CORE phase

Parameter \ Visit	Baseline Pasi/Octreo	Mos 3 Pasi/Octreo	Mos 6 Pasi/Octreo	Mos 9 Pasi/Octreo	Mos 12 Pasi/Octreo
Absolute Lymphocytes % > ULN %< LLN					
Absolute neutrophils (Seg. + Bands) % > ULN %< LLN					
Activated partial thromboplastin time % > ULN %< LLN					
Hemoglobin % > ULN %< LLN					
Platelet Count % > ULN %< LLN					
Prothrombin Time (INR) % > ULN %< LLN					
WBC (total) % > ULN %< LLN					

Pasi, pasireotide LAR; Octreo, Octreotide LAR; Mos, month; ULN, upper limit normal; LLN, lower limit normal

8. Please create similar tables to Table 6 and 7 for biochemistry parameters (excluding glucose, AST, ALT, Alk Phos, GGT and bilirubin) listed in Table 12-26 on page 218-219 of the Study CSOM2305 Clinical Study Report. Provide this data for Study CSOM 2402 as well.
9. Provide unique subject identifiers and narratives for those patients with any grade 3 or 4 hematologic or biochemistry abnormality excluding glucose, ALT, AST, Alk phos, GGT and bilirubin for Studies CSOM2305 and 2402.
10. In the dataset AAEV for study CSOM2305, please define:

- 0 and 1 in column EXTN
- "9" in column TRTXN
- crossed (1) and not crossed (0) definitions in the column AEVSER1C

11. Many patients experienced a dose delay over the course of the study. Provide a table that includes the average number of days \pm SD (range) a dose was delayed for each visit as well as the number of patients in the CORE phase by treatment group using the shell below. If all of the dose delays were within the \pm 2 day dosing period, confirm this and the table will not be needed. Please do this for both Studies CSOM2305 and 2402.

Table 9. Dose delay

<u>Visit</u> <u>Parameter</u>	Baseline	Mos 0.5	Mos 1	Mos 1.5	Mos 2	Mos 3	Mos 4	Mos 5	Mos 6	Mos 7	Mos 8	Mos 9	Mos 12
Pasi													
Mean # days delayed \pm SD (range)													
# patients (%) with delay													
Octreo													
Mean # days delayed \pm SD (range)													
# patients (%) with delay													

12. We have reviewed the SAE listings and narratives provided in the Clinical Study Report (CSR) as well as in the Integrated Summary of Safety (ISS) for CSOM2305. We would expect all SAE listings/narratives in the CSR to also be present in the ISS for CSOM2305. In addition, the ISS would contain SAE occurrences after the Dec 29, 2011 data-cut off for the CSR CSOM2305. However, there appear to be several SAE listings/narratives in the CSR which are not listed in the ISS. Also, in the ISS, it is not clear which study drug the patient was taking, whether or not they crossed over and in what phase the SAE occurred. Please explain why there are SAE listings in the CSR that are not represented in the ISS and modify the ISS listings accordingly. Also modify the ISS SAE narratives (those not represented in the CSR) such that they are in the format presented in the CSR. Confirm that the SAE listings in the Clinical Study Report for Study CSOM2402 all correspond to the SAE listings in the ISS with additional SAE listings in the ISS as appropriate for data cut-off. For Study CSOM2402, please also modify the ISS SAE narratives (those not represented in the CSR) such that they are in the format presented in the CSR.

13. Please explain the discrepancy in the numbers of patients listed in Table 5-16 (page 129 of CSR 2305) and Table 2-1 (page 3 of Response to FDA Information Request received 30-Jul-2012 as seen below). These tables appear to represent the same time periods in Study CSOM2305; however, in Table 5-16, n= 53 and n=65 patients qualify as ALT or AST >ULN and \leq 3x ULN in the pasireotide and octreotide LAR groups, respectively.

Yet, in Table 2-1 the respective numbers are n=62 and n=71. Explain this and other discrepancies seen between these two tables.

Table 5-16 Categorical liver function test outliers in medically naïve patients – Study C2305 up to crossover (SAS)

Categorical LFT outliers	Pasireotide LAR	Octreotide LAR
	N=178 n (%)	N=180 n (%)
ALT or AST >ULN and ≤ 3xULN	53 (29.8)	65 (36.1)
ALT or AST >3xULN	9 (5.1)	6 (3.3)
ALT or AST >5xULN	1 (0.6)	1 (0.6)
ALT or AST >10xULN	1 (0.6)	0
TB>ULN and <2xULN	33 (18.5)	40 (22.2)
TB ≥ 2xULN	4 (2.2)	5 (2.8)
Hy's law	0	0

Categories are based on worst post-baseline value for any specific parameter

Hy's law refers to a concomitant elevation of ALT or AST >3xULN with TB ≥ 2xULN and ALP <2xULN

Source: [SCS-Appendix 1–Table 4.1-1].

VERSUS

Table 2-1 Number (%) of patients with elevations of liver chemistry by treatment up to cross over in Study CSOM230C2305

Study C2305	N	ULN<AxT≤ 3xULN n (%)	AxT >3xULN n (%)	AxT >5xULN n (%)	AxT >10xULN n (%)	AxT >20xULN n (%)	Tbili >ULN to <2xULN n (%)	Tbili ≥2xULN n (%)	AxT >3xULN , Tbili ≥2xULN, AP <2xULN n (%)
Pasireotide LAR	178	62 (34.8)	9 (5.1)	1 (0.6)	1 (0.6)	0	37 (20.8)	4 (2.2)	0
Octreotide LAR	180	71 (39.4)	6 (3.3)	1 (0.6)	0	0	45 (25.0)	5 (2.8)	0

AxT= Aminotransferases, ALT or AST
Source: [Appendix 1 - Study CSOM230C2305 Table 4.1-1]

14. In the ISS, Table 3.1-57 provides the results of a logistic regression analysis of possible risk factors for developing hyperglycemia. Provide this analysis using only the CORE phase data from Study CSOM2305.

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/s/

JENNIFER L JOHNSON

03/17/2014

Clinical information requests from Smita Abraham and team leader Dragos Roman



NDA 203255

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation
Attention: Rose Gao, MS
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gao:

Please refer to your New Drug Application (NDA) dated and received November 15, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Signifor LAR (pasireotide) intramuscular injection, 20 mg, 40 mg, 60 mg.

We also refer to your amendment dated December 23, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **September 15, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **August 18, 2014**.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

Chemistry/Biopharmaceutics

1. Your proposed dissolution acceptance criteria are not adequate. (b) (4)
The range of the acceptance criteria at any dissolution time point should be $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Modify the proposed dissolution acceptance criteria according to this principle. Provide the dissolution data of the available batches, including the dissolution values for individual unit, the mean, the standard deviation (or CV%) and the plot.

2. It is stated that the purpose of performing *in vitro/in vivo* correlation (IVIVC) investigation includes elaborating potential biorelevance of the *in vitro* drug release methods. However, the information for IVIVC to support the *in vitro* drug release method and acceptance criteria was not submitted. Provide the detailed IVIVC report, including the datasets for the *in vitro*, *in vivo* and the correlations in SAS transport file format. Submit the justifications for the *in vitro* drug release method and the proposed acceptance criteria.

3. (b) (4)

Device

4. You have stated that you intend to use the Medimop Medical Projects Mixject Dispensing pin with detachable vial holder with preattached needle (K963583) with the (b) (4) syringe system. However, not all of the testing has been provided to demonstrate the safety of this device with your drug. Provide a complete test report (including protocol, acceptance criteria, results and conclusion) for the following testing:

- Demonstrate that the vial adapter/syringe doesn't result in air or liquid leakage.
- Provide torque testing force necessary to disconnect the syringe's (b) (4) connection from the vial adapter.
- Provide the force necessary to draw up Signifor LAR (pasireotide) in the syringe.
- Provide the break loose and glide force of the syringe for injection.

Clinical/Statistics

5. Protocol amendments 1 (section 2.56) and 4 (section 2.51) to Study CSOM2305 and protocol amendment 1 (section 10.4.3) to Study CSOM 2402 make changes to the definition of missing data. In reference to those changes, please explain: 1) why the "within 15-day limit that would consider GH and IGF-1 as being missing" was removed, and 2) why a "35-day limit that would consider GH and IGF-1 as being missing for any LAR injection" is acceptable, as the Signifor LAR injections were given every 28 days. Provide the protocol-specified windows of collecting GH and IGF-1 data at Visits 1, 2, 7, 10, 13 and EOS Core.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There must be no white space between the Highlights Heading and Highlights Limitation Statement. Please remove the white space that is currently present between the Highlights Heading and the Highlights Limitation Statement.
2. The preferred presentation for cross-references in the Full Prescribing Information is the section (not subsection) heading followed by the numerical identifier. There are two instances in which the preferred presentation was not used, both in subsection 5.2, Bradycardia and QT Prolongation, of the Warnings and Precautions section.
 - a. The cross-reference [REDACTED] (b) (4) should be revised to read *[see Clinical Pharmacology (12.2)]*.
 - b. The cross-reference [REDACTED] (b) (4) should be revised to read *[see Clinical Pharmacology (12.2)]*.

We request that you resubmit labeling that addresses these issues by February 18, 2014. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), patient PI and healthcare provider instructions for use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient PI and healthcare provider instructions for use (IFU), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
01/28/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203255

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ATTENTION: Rose Gao, M.S.
Director, Drug Regulatory Affairs

Dear Ms. Gao:

Please refer to your New Drug Application (NDA) dated November 14, 2013, received November 15, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pasireotide for Injection, 20 mg/vial, 40 mg/vial, and 60 mg/vial.

We also refer to your November 14, 2013, correspondence, received November 15, 2013, requesting review of your proposed proprietary name, Signifor LAR. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your November 14, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, M.S., M.B.A., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Jennifer Johnson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/27/2014

From: Johnson, Jennifer
To: [Gao, Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: Johnson, Jennifer
Subject: NDA 203255 (Signifor LAR): Clinical Pharmacology Information Request
Date: Friday, January 24, 2014 11:20:00 AM

Dear Rose,

We could not locate the study reports and supporting materials for the population PK and PK/PD modeling analysis (PD, efficacy, safety) as referenced in section **1.2 Summary of overall conclusion** and **4.3 Exposure-response relationship** from the '2.7.2 Summary of Clinical Pharmacology'.

Please submit full study reports along with model codes, analysis datasets and define files for these study reports. If already submitted in the original NDA, please point us to the correct location. Refer to the following link regarding general expectations for submitting pharmacometric data and models.
(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>)

If you could respond by close of business on January 30th, we would greatly appreciate it. Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Phone: (301) 796-2194
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/s/

JENNIFER L JOHNSON

01/24/2014

Information request from pharmacometrics reviewer Lian Ma (TL concurrence from Nitin Mehrotra)

From: Johnson, Jennifer
To: [Gao_Rose \(rose.gao@novartis.com\)](mailto:rose.gao@novartis.com)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 203255 (Signifor LAR): Information Request
Date: Monday, December 16, 2013 7:15:00 PM

Dear Rose,

We will need further information in the event that inspections are needed for NDA 203255, Signifor LAR, submitted on November 15, 2013.

The datasets submitted with the application for pivotal Studies CSOM230C2305 and CSOM230C2402 were not complete, and are missing the following 19 variables:

STUDYTL
DOMAIN
SPONNO
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COUNTRY
STATE
CITY
POSTAL
STREET

These missing variables will be necessary in order to pass the first validation step of the dataset processing. We note that your instructions included in the reviewer's guide for merging the data is to convert the pdf to Excel format. This is not feasible at the time because (1) it would be more time-consuming to convert to Excel first because manual extraction is still required whether it is in pdf or Excel format, and (2) we generally refrain from making changes to the original sponsor-submitted dataset as the process of manually copying and pasting the data for more than 100 sites could introduce an error.

Please submit updated datasets including the missing 19 variables as an amendment to NDA 203255 as soon as possible.

For additional guidance regarding this request, see the following links:

Guidance for Industry: Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ucm332466.pdf>

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
12/16/2013



NDA 203255

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Rose Gao, MS
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gao:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Signifor[®] LAR (pasireotide) injection; 20 mg, 40 mg, 60 mg

Date of Application: November 15, 2013

Date of Receipt: November 15, 2013

Our Reference Number: NDA 203255

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **January 14, 2014**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JENNIFER L JOHNSON
12/02/2013



IND 074642

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Rose Gao, M.S.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gao:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOM230C (pasireotide) LAR intramuscular injection.

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2013. The purpose of this Pre-NDA follow-up guidance meeting was to discuss additional new data for inclusion in your upcoming NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Type C Guidance Meeting Minutes for SOM230C (pasireotide) LAR IM Injection



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance (Pre-NDA follow-up meeting)

Meeting Date and Time: Monday, September 9, 2013; 12:00 – 1:00 pm
Meeting Location: CDER, White Oak Campus

Application Number: IND 074642
Product Name: SOM230C (pasireotide) LAR intramuscular injection
Indication: Treatment of acromegaly
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Acting Director
Dragos Roman, M.D.	Clinical Team Leader
Naomi Lowy, M.D.	Clinical Reviewer
Julie Van der Waag MPH	Chief, Project Management Staff
Jennifer Johnson	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics II

Mark Rothmann, Ph.D.	Team Leader
Dongmei Liu, Ph.D.	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Representing Novartis Pharmaceuticals Corporation

Germo Gericke, M.D.	Global Program Head Oncology
Karina Hermosillo, M.D.	Director Clinical Research
Alberto Pedroncelli, M.D.	Global Medical Brand Director Clinical Research
Sibylle Jennings, Ph.D.	Global Program Regulatory Director

Shanthi Ganeshan, Ph.D.	North America Region Head Drug Regulatory Affairs
Rose Gao, M.S.	Director, Drug Regulatory Affairs
Mike Hu, Ph.D.	Sr. Fellow Clinical Pharmacologist
YinMiao Chen, Ph.D.	Expert Statistician
William Ludlam, M.D.	Director Clinical Research, US CDMA-Rare Disease II
Mounir Aout, Ph.D.	Senior Statistician
Shoba Ravichandran, M.D.	Executive Director Clinical Research

1.0 BACKGROUND

The sponsor submitted a request for this Type C pre-submission guidance meeting on July 2, 2013, for SOM230C (pasireotide LAR) intramuscular injection, as a follow-up to the Pre-NDA meeting held with the sponsor on November 29, 2011 (meeting minutes issued on December 20, 2011). A meeting granted letter issued on July 22, 2013.

This somatostatin analog is being developed to treat patients with acromegaly [REDACTED] (b) (4). Currently approved drug treatments for acromegaly include Sandostatin Injection (octreotide acetate), Sandostatin LAR Depot (octreotide acetate) and Somatuline Depot (lanreotide) Injection, all of which are also somatostatin analogs. Proposed advantages to the pasireotide formulation include a higher binding affinity to all five somatostatin receptors, as well as a more pronounced IGF-1 suppression.

The purpose of this follow-up pre-submission meeting is to discuss additional new data from pivotal clinical study C2402, entitled, "A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly." The sponsor plans to include this data in its upcoming NDA submission, along with data from pivotal clinical study C2305, entitled "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly." Study C2305 was discussed during the Pre-NDA meeting held on November 29, 2011.

The sponsor intends to submit a new drug application (NDA) 203255 in April 2012, supported mainly by these two pivotal clinical studies, along with data cross-referenced from NDA 200677, Signifor (pasireotide) subcutaneous injection (short-acting formulation), approved on December 14, 2012, for the treatment of patients with Cushing's disease. The planned dosages for pasireotide LAR are 20 mg, 40 mg and 60 mg, administered every 28 days.

This drug is also being developed for the treatment of patients with Cushing's disease under this IND (and under IND 068635, the IND corresponding to approved NDA 200677), [REDACTED] (b) (4)

Pasireotide received orphan designation on August 25, 2009, for the treatment of acromegaly.

On January 20, 2011, the sponsor submitted a request for review of its proposed proprietary name for this product, Signifor LAR. On July 19, 2011, a conditionally acceptable letter issued. The sponsor should submit a request for review of the proprietary name again once the NDA is submitted.

The sponsor submitted a meeting briefing document on August 6, 2013. Preliminary responses were sent to the sponsor via secure e-mail on September 5, 2013. During the meeting discussion, FDA requested additional clarification regarding certain components of the sponsor's planned

NDA submission. The sponsor sent a post-meeting response document via e-mail on September 26, 2013, and via official electronic submission on October 3, 2013.

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), followed by the sponsor's response and the meeting discussion, and where applicable, the post-meeting comments (bolded/italicized).

Clinical Safety and Efficacy/Clinical Pharmacology

Question 1: Novartis considers that the data based on the two pivotal studies, CSOM230C2305 and CSOM230C2402, is robust and adequately supports the intended proposed indication "treatment of patients with acromegaly (b) (4)". Does the Agency agree?

FDA Preliminary Response: As discussed in the first pre-NDA meeting, Study 2305 appears to support the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or for whom surgery is not an option. Whether Study 2402 additionally supports the treatment of patients who are inadequately controlled on medical therapy is a review issue, and clearly a comprehensive evaluation of the efficacy and safety of this product will inform that decision.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

Question 2: Data inclusion pooling in support of Summary of Clinical Safety (SCS), Summary of Clinical Efficacy (SCE) and Summary of Clinical Pharmacology:

- a. Novartis considers that no pooling of efficacy is required for the SCE, does the Agency agree?

FDA Preliminary Response: Yes, we agree.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

- b. Novartis considers that safety pooling of the patients treated with pasireotide LAR with inadequate response to other SSAs from studies CSOM230C2402 core phase and CSOM230C2305 crossover phase is appropriate to support the Summary of Clinical Safety (SCS). Does the Agency agree?

FDA Preliminary Response: Although there are similarities between the 2 populations you describe, there are also key differences. One such prominent difference is that the population in Study 2402 may have had prior pituitary

surgery. Therefore, you may pool the safety data from these similar populations, but the safety data from the individual trials will also be strongly considered in the NDA review.

Sponsor Response/Meeting Discussion: *See slide 5 of sponsor slide presentation. The sponsor stated that the NDA submission will be based on individual safety data from C2305 and C2402. Key safety outputs are pooled for inadequately controlled patients (C2305 crossover and C2402 core), and both studies include pre-surgery and post-surgery patients.*

FDA asked what percentage of patients had pituitary surgery in each trial. The sponsor said that Study 2402 had approximately 70% of patients with prior pituitary surgery and Study 2305 had 40.3% with previous pituitary surgery. (Refer to slides 4-5 of the sponsor's back-up slide presentation during the meeting, which detail previous surgery in patients treated with pasireotide in studies C2305 and C2402.)

FDA also sought clarification regarding the differences between the two studies (i.e., Study C2305 patients started the trial treatment-naïve and then were treated for one year; Study C2402 patients were treated for 6 months with other somatostatin analogs before crossing over to pasireotide LAR). The sponsor stated that they believe there are no differences between the two patient populations. FDA said that it wants to understand what will be presented in the tables. The sponsor stated that their intent is to include tables depicting side-by-side results from both studies (individual and pooled in the cross-over phase).

- c. Does the Agency agree with the proposed pooling strategy for data analyses in support of the Summary of Clinical Pharmacology (SCP)?

FDA Preliminary Response: Yes, this appears to be acceptable. If there are any additional comments, they will be conveyed during the meeting.

Sponsor Response/Meeting Discussion: *The sponsor asked if FDA had any further comments to convey regarding the SCP pooling strategy. FDA told the sponsor to include the study (i.e., Study C2305 and C2402) as a covariate in the pooled PK/PD data analysis as patient populations are different between studies. The sponsor stated that the two patient populations in the crossover part of Study C2305 and the patient population in Study C2402 were similar for the PK/PD safety analysis, and that they will clarify which covariates were included in the pooled modeling in the NDA submission. FDA asked if the sponsor planned to include the two studies as a covariate in their pooled model, and said that it could be beneficial to include them. The sponsor said that they will consider this and follow up with FDA if it is needed.*

Post-Meeting Comments: *The sponsor provided the following clarification via e-mail on September 26, 2013 (and followed up with an official electronic submission on October 3, 2013):*

PK/PD analyses were conducted for efficacy and safety in individual studies for medically naïve patients (study C2305) and inadequately controlled patients (study C2402). Demographics (e.g. race, gender, age, body weight, etc.), baseline liver function tests [such as ALT (alanine aminotransferase), AST (aspartate aminotransferase), TB (total bilirubin), GGT (gamma-glutamyltransferase), ALP (alkaline phosphatase) and albumin], baseline renal function [creatinine clearance based on Cockcroft-Gault (CG) equation, or estimated glomerular filtration rate (eGFR) based on the modification of diet in renal disease equation], and baseline disease status (baseline GH and IGF-1 levels) were explored as potential covariates in PK/PD analyses in individual studies C2305 and C2402, respectively. Pooled PK/PD analyses were conducted for safety in inadequately controlled patients from study C2402 core phase and study C2305 crossover phase. Demographics and lab tests mentioned above were explored as potential covariates in pooled PK/Safety analyses. Please note that neither dose nor study were included as a covariate in pooled PK/Safety analyses per original analysis plan due to the following reasons:

- *Dose: in general, dose is only included in dose-exposure models but not in exposure-response models as exposure does not explain dose (it's the opposite). Therefore, exposure is taken as given to explain response. This is particularly important as concentrations may change over time due to dose titration and intra-patient variability across visits.*
- *Study: Since inadequately controlled patients from study C2402 and study C2305 crossover phase were considered similar, "study" was not included as a covariate in the original analysis plan for pooled PK/Safety analyses. In response to the question from FDA at the meeting, Novartis has included study effect in post-hoc analyses. Results show that "study" (C2402 vs. C2305 crossover) was not a statistically significant covariate in critical safety parameter analyses, such as PK/hyperglycemia (logistic regression and proportional odds models), PK/QTcF, or PK/LFT (ALT, AST and TB) analyses. It appeared that study (C2402 vs. C2305 crossover) had a shift in the intercept in PK/QTcB and PK/LFT (ALP, GGT and albumin), but the shape (slope) of these relationships did not change, suggesting that study (C2402 vs. C2305 crossover) is not a critical factor for the exposure-response relationship in statistical models.*

FDA Response to Sponsor's Post-Meeting Clarification: *The sponsor's post-meeting response reasonably addresses FDA's comment during the meeting. Details of the clarification are review issues.*

Question 3: Does the Agency agree with the statistical analysis plan for the CSOM230C2402 study, in particular, with the procedure for testing the primary and key secondary endpoints?

FDA Preliminary Response: We agree with the proposed procedure for testing the primary and key secondary endpoints.

For handling of missing data, you propose for a patient with missing values of mean GH or IGF-1 at 24 weeks or who withdraws earlier from the study will be considered as a non-responder with sensitivity analysis using last observation carried forward (LOCF) as missing data imputation for the primary key secondary endpoints. The method for handling missing data (i.e., loss to follow-up) in the primary analysis should discuss what assumptions went into the choice of method. The reasonableness of the assumptions should be assessed statistically. For further advice on missing data refer to the following report: National Research Council of the National Academies of Science. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, D.C.: National Academies Press, 2011.

Sponsor Response/Meeting Discussion: Refer to slides 6-7 of sponsor slide presentation regarding the handling of missing data for the primary endpoint in Study C2402. FDA sought clarification that missing data for the primary endpoint in Study C2305 was handled in the same way. The sponsor replied that in Study C2305 a similar approach was used. The sponsor stated that patients with missing data were considered non-responders, and FDA advised the sponsor to include their reasoning in the NDA submission. FDA told the sponsor that the LOCF imputation method for missing data is not recommended anymore, and pointed to the cited report in the Preliminary Response to this question. The sponsor acknowledged that FDA does not recommend the LOCF imputation method for the primary analysis but that the FDA guidance mentions an allowance for scientific adjustment; these issues will be addressed in the NDA submission.

FDA reminded the sponsor that the sponsor's approach to handling missing data would be a review issue. The sponsor reiterated that explanations for missing data in the LOCF-treated patients would be included in the NDA submission.

Question 4: Safety Updates

- a. Does the Agency agree to the cut-off date proposed for the safety update?

FDA Preliminary Response: Please clarify for each study, in tabular form, how much data will be included in the Safety Update.

Sponsor Response/Meeting Discussion: See slides 12-14 of sponsor slide presentation. The sponsor plans to include in the NDA submission exposure, disposition, concomitant medication and key safety tables including AEs, lab, QT/QTc and liver parameters. In response to these slides, FDA clarified that the intent of this question was to understand the timelines associated with the data cut-off. Discussions and clarifications were provided by the sponsor and the sponsor said they would submit this information to FDA in tabular form for each study and for each portion of each study (core and extensions).

After the meeting, in response to the FDA request, the sponsor submitted via email on September 26, 2013 the following table that outlines the safety data cut-off information for the original NDA and the safety update.

Study	Study design	Original NDA	Safety update
[C2305] (Ongoing)	Phase 3, blinded, active-controlled, randomized study of pasireotide LAR vs. octreotide LAR in patients with acromegaly to assess efficacy, safety, QoL, PK, and PK/PD relationship	Data cut-off: 29-Dec-2011 Data included: <ul style="list-style-type: none"> Up to crossover: at least 26 month data unless early discontinuation or crossed-over to the other treatment group for patients in pasireotide LAR and octreotide LAR groups After crossover: at least 13 month data unless early discontinuation for patients in pasireotide LAR and octreotide LAR groups 	Data cut-off: 3-Jun-2013 Additional data included compared with original NDA: <ul style="list-style-type: none"> Up to crossover/after crossover: additional 18 month data, unless early discontinuation, for patients in pasireotide LAR group <p>Note: per study design, patients receiving octreotide LAR were not allowed to continue in the study after month 26.</p>
[C2402] (Ongoing)	Phase 3, double-blind 40 mg or 60 mg pasireotide LAR vs. open-label octreotide LAR or lanreotide ATG in patients with acromegaly to assess efficacy and safety	Data cut-off: 6 months for each patient (last patient last visit for core phase is 22-Jan-2013) Data included: 6 month data (core phase)	Data cut-off: 3-Jun-2013 <ul style="list-style-type: none"> Additional 1 month for patients receiving octreotide LAR or lanreotide ATG <p>Note: per study design, patients receiving octreotide LAR or lanreotide ATG would either switch to pasireotide LAR 40 mg or discontinue from the study after month 7.</p> <ul style="list-style-type: none"> Additional maximum 23 months data (approximately) for patients continuously receiving or switching to pasireotide LAR
[C2110E] (Ongoing)	Open-label extension of Study C2110 to assess long-term safety and PK/PD profiles in patients with acromegaly or carcinoid disease ^b	Data cut-off: 14-Jan-2011 Data included: all data collected up to data cut-off 16 acromegaly patients ongoing as of the date of data cutoff	Data cut-off: 30-Jul-2013 Additional maximum 30 months data for 16 ongoing acromegaly patients at the previous cutoff
[B2201E3] (Ongoing)	Open-label extension of Study B2201 to assess long-term safety, efficacy, and PK	Data cut-off: 30-Dec-2010 6 patients ongoing as of the date of data cutoff	Data cut-off: 30-Jul-2013 Additional maximum 31 months data for 6 patients ongoing at the previous data cutoff

- b. Does the Agency agree with the content of the proposed safety updates?

FDA Preliminary Response: Yes.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

- c. Does the Agency agree on the proposed timing for submission in case of Priority Review?

FDA Preliminary Response: Yes.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

- d. Does the Agency agree that the safety update will not be considered as a substantial amendment under the framework of PDUFA V?

FDA Preliminary Response: Please clarify if you are asking about whether this would be a major amendment.

Sponsor Response/Meeting Discussion: Refer to slide 8 of sponsor slide presentation. The sponsor said that they intend to submit the standard safety update as per regulations and would like to clarify that this safety update will not be considered by FDA to be a major amendment. FDA replied that safety updates are not considered to be major amendments.

Question 5: In the context that phase III study CSOM230C2402 will be included in the NDA, Novartis plans to submit case report tabulations (CRT) for study CSOM230C2402, SCS and SCP in addition to the previously agreed CRTs for CSOM230C2305. Furthermore, Novartis will also provide the analysis programs for the analysis of the primary and key secondary endpoints, along with the programs used to generate the derived efficacy datasets for the pivotal phase III study CSOM230C2305. Does the Agency agree that this plan satisfied the requirements of 21 CFR 314.50(f)(1)?

FDA Preliminary Response: This plan is acceptable. You mentioned that you will provide the analysis program for study CSOM230C2305. Please clarify if you also plan to provide the analysis program for the analysis of the primary and key secondary endpoints, along with the programs used to generate the derived efficacy datasets for the pivotal phase III study CSOM230C2402.

Sponsor Response/Meeting Discussion: *See slide 15 of sponsor slide presentation. The sponsor confirmed that the NDA submission will include the analysis program for the primary, key secondary endpoints, along with the programs used to derive the efficacy datasets for C2402. FDA said that this was acceptable.*

Question 6 (Follow-up question for CRT): Does the Agency agree with Novartis' proposal for the submission of electronic datasets?

FDA Preliminary Response: Yes, it is acceptable.

Sponsor Response/Meeting Discussion: *No discussion took place; Novartis accepts FDA preliminary response.*

FDA Post-Meeting Comments:

The [PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017](#) guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. The sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization ([CDASH](#)) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the [CDER Common Data Standards Issues Document](#) for further information on data standardization in submissions.

Regulatory/Administrative

Question 7: Does the Agency agree that the content described in the draft NDA Table of Contents together with the information provided in this briefing document is acceptable to support filing of a complete NDA?

FDA Preliminary Response: Yes.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

Question 8: Novartis plans to follow the guidance as outlined in the Pre-NDA meeting minutes for acromegaly's NDA 203255 (dated 20-Dec-2011). Does the Agency agree with the proposal?

FDA Preliminary Response: Yes. We note that in Appendix 10, Bioresearch Monitoring (BIMO) Document, under "Section III Request for Site Level Data for the risk based model", you state "Due to publishing software limitations, we could not follow the file structure exactly". For ease of inspection preparation by the Office of Scientific Investigations, please use the naming convention as outlined in the draft guidance "Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning" for the dataset (i.e., clinsite.xpt).

Sponsor Response/Meeting Discussion: See slide 16 of sponsor slide presentation. Novartis will follow the naming convention as outlined in the draft guidance "Providing Submissions in Electronic Format – Summary Level Clinical Data for CDER's Inspection Planning" for the dataset (i.e., clinsite.xpt). FDA acknowledged and agreed with the sponsor's plan.

Question 9: Novartis intends to request a priority review based on FDA guidance in that it demonstrates a significant improvement compared to marketed products in the treatment. We understand that the decision for the priority review is made at the time of NDA filing; does the Agency have comments on the justification provided as a basis for the priority review?

FDA Preliminary Response: No.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

Question 10: Does the Agency agree that pasireotide LAR will be considered as non-NME for the acromegaly NDA submission?

FDA Preliminary Response: Yes.

Sponsor Response/Meeting Discussion: No discussion took place; Novartis accepts FDA preliminary response.

Additional Clinical/Regulatory Comments:

1. In Study 2305, the maximum dose for octreotide LAR was 40 mg. Please clarify why this was chosen as the maximum dose as the package insert allows for titration up to 40 mg.

Sponsor Response/Meeting Discussion: Refer to slide 9 of sponsor slide presentation. FDA asked the sponsor if currently labeling (outside the U.S.) specifies 30 mg as the highest approved dose. The sponsor replied that some countries outside the U.S. have approved 40 mg as the highest dose, and that obtaining approval in other countries is an ongoing process. FDA reminded the sponsor to clearly state the rationale for dose selection in the analyses provided in the NDA submission, and the sponsor agreed.

2. Although your proposed proprietary name Signifor LAR was previously found to be conditionally acceptable (refer to our letter dated July 19, 2011), you should submit another request for proprietary name review in your NDA submission.

Sponsor Response/Meeting Discussion: See slide 17 of sponsor slide presentation. Novartis will submit a proprietary name review request in the NDA submission. FDA acknowledged this response.

Additional Meeting Discussion Regarding Hyperglycemia Management:

Given the expectation that pasireotide administration induces elevated glucose levels, FDA advised the sponsor to follow the same general approach for presenting the data on glucose levels and hyperglycemia management in the NDA submission as they did in the briefing document and in their presentation at the Advisory Committee Meeting held on November 7, 2012 (discussion of NDA 200677, approved on December 14, 2012, for the treatment of patients with Cushing's disease). The sponsor's presentation during this meeting included description of changes in patients' glycemic levels during the clinical trial and the shift between patient groups and categories. Graphic representations of the data and capturing individual changes across glycemic thresholds are strongly encouraged. FDA told the sponsor to clarify the difference in glucose level deterioration for those patients who were on medical treatment prior to starting the study and for those who were *de novo*. The sponsor asked if this applies to Study C2305 only, and FDA replied yes.

The sponsor told FDA that in their analysis of Study C2402 they observed that investigators who were more familiar with anti-diabetic medications tended to act more promptly in treating patients with elevated glucose levels, as opposed to less familiar investigators who tended to rely on a wait-and-see approach to treatment. FDA asked the sponsor to separate these data for FDA in the NDA submission, if feasible, and the sponsor agreed to make such an attempt.

FDA asked if there were differences in glycemic management among Cushing's and acromegaly patients in the clinical trials. The sponsor stated that there were differences based on the formulation (pasireotide short-acting versus pasireotide long-acting),

underlying diseases and information and experience that the investigators have in treating hyperglycemic patients. They found that the prevailing factor was the experience and knowledge of the investigators; the more knowledge and experience an investigator had, the more quickly he/she was likely to intervene with anti-diabetic treatment. Given the experience gained in treatment of Cushing's patients, as well as treatment of acromegaly patients in Study C2305, the sponsor had a much better understanding of hyperglycemia management when designing Study C2402. This clinical trial protocol was updated based on mechanistic studies conducted in the Cushing's disease population; this information was applied to their study of acromegalic patients. Thus, the time to intervention in hyperglycemic management improved in Study C2402.

FDA asked which anti-diabetic agents were most commonly used. The sponsor replied that metformin was the most commonly used agent, and then if necessary, patients were switched to a GLP-1 or DPP-4 analog (or the chosen analog was added on to metformin treatment). In Study C2402, some patients were treated for a long time with both anti-diabetic agents and somatostatin analogs. When Study C2305 was conducted, the sponsor did not have data from mechanistic studies to better inform investigators on how to manage patient hyperglycemia. FDA asked the sponsor to explain this in the NDA submission. The sponsor agreed, and added that with ongoing Study B2319 they are continuing to obtain additional information. One observation noted thus far was that investigators tended to be reluctant to be guided on hyperglycemia management; instead, they believed that individual patient characteristics should prevail over established treatment guidelines. The sponsor also pointed out that glucose level alteration was not a feature unique to pasireotide but rather common with all somatostatin analogs (including octreotide and lanreotide).

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the

Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

The sponsor was asked to submit further explanation regarding:

- The study safety data cutoff points for both pivotal Phase 3 studies.
- Whether blinded and unblinded data will be assessed separately.
- Covariates used in the pooled PK/PD analyses, and whether the study and dose were considered as covariates in SCP pooling.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor PowerPoint slide presentation.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
10/10/2013



IND 074642

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Michelle Hack
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Hack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOM230C (pasireotide LAR) IM Injection.

We also refer to the meeting between representatives of your firm and the FDA on Tuesday, November 29, 2011. The purpose of the meeting was to discuss the filing requirements for this product for the treatment of patients with acromegaly.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA Version of Pre-NDA Meeting Minutes for SOM230C (pasireotide LAR) IM Injection



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, November 29, 2011, 12:00 - 1:00 pm
Meeting Location: CDER, White Oak Campus

Application Number: IND 074642
Product Name: SOM230C (pasireotide LAR) IM Injection
Indication: Treatment of patients with acromegaly
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Mary H. Parks, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Mary Parks, M.D.	Director
Dragos Roman, M.D.	Clinical Team Leader
Naomi Lowy, M.D.	Clinical Reviewer
Ali Mohamadi, M.D.	Clinical Reviewer
Amy Egan, M.D., M.P.H.	Deputy Director for Safety
Karen Davis Bruno, Ph.D.	Pharmacology/Toxicology Supervisor
Miyun Tsai-Turton, Ph.D.	Pharmacology/Toxicology Reviewer
Julie Marchick, M.P.H.	Acting Chief, Project Management Staff
John Bishai, Ph.D.	Safety Regulatory Project Manager
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Jayabharathi Vaidyanathan, Ph.D.	Acting Clinical Pharmacology Team Leader
Zhihong Li, Ph.D.	Clinical Pharmacology Reviewer

Office of Translational Sciences, Office of Clinical Pharmacology, Division of Pharmacometrics

Nitin Mehrotra, Ph.D.

Pharmacometrics Reviewer,
QT-IRT Scientific Lead

Office of Biostatistics, Division of Biometrics II

J. Todd Sahlroot, Ph.D.

Deputy Director and Team Leader

Janice Derr, Ph.D.

Biometrics Reviewer

Office of Pharmaceutical Science, New Drug Microbiology Staff

Robert Mello, Ph.D.

Microbiology Reviewer

Office of Surveillance and Epidemiology

Ermias Zerislassie

Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management, Division of Risk Management

Cynthia LaCivita, Pharm.D.

Drug Risk Management Analyst

Office of Orphan Products Development

Jeff Fritsch, R.Ph.

Regulatory Review Officer

SPONSOR ATTENDEES

Representing Novartis Pharmaceuticals Corporation

Gabriela Gruia, M.D.

SVP & Global Head Drug Regulatory Affairs,
Oncology

Lynne McGrath, M.P.H, Ph.D.

Vice President, NA Head Drug Regulatory Affairs,
Oncology

Sibylle Jennings, Ph.D.

Global Program Regulatory Director

Michelle Hack, RAC

Associate Director, Drug Regulatory Affairs

Dagmar Wirth, Ph.D.

Global Regulatory CMC Liaison

Germo Gericke, M.D.

Global Program Head, Oncology

Pharis Mohideen, M.D.

Global Clinical Program Head

Karina Hermosillo Resendiz, M.D.

Global Clinical Leader

Johannes Eisinger, M.D.

Leader Brand Safety Leader

Mike Hu, Ph.D.

Sr. Fellow Clinical Pharmacologist

Li Li, Ph.D, DABT

Director, Preclinical Safety

Antonella Maniero, Ph.D.

Senior Unit Head Biostatistics Clinical
Development

Yin-Miao Chen, Ph.D.

Expert TA Statistician

Sophie Jauffret, M.S.

Expert Statistician

Kris Grzegorzewski, M.D.

Sr. Medical Director, US CDMA Oncology

1.0 BACKGROUND

The sponsor submitted a meeting request for this Type B Pre-NDA meeting on September 2, 2011, to discuss the filing requirements for SOM230C (pasireotide LAR) intramuscular injection. This somatostatin analog is a new molecular entity being developed to treat patients with acromegaly (b) (4). A meeting granted letter issued on September 22, 2011.

This drug is also being developed for the treatment of patients with Cushing's disease. An End-of-Phase 2 (EOP2) meeting was held on February 15, 2011, for this indication, and meeting minutes issued on March 17, 2011. Clinical studies have been conducted in the Cushing's population with the short-acting pasireotide (SOM230B) subcutaneous (s.c.) injection formulation as well, under IND 068635 (related IND for NDA 200677, which was submitted for marketing approval on June 21, 2011, and withdrawn by the sponsor on August 19, 2011; the sponsor plans to resubmit NDA 200677 during the first quarter of 2012). The sponsor is also conducting clinical studies in the acromegaly patient population with this formulation under the same IND (b) (4).

Currently approved drug treatments for acromegaly include Sandostatin Injection (octreotide acetate), Sandostatin LAR Depot (octreotide acetate) and Somatuline Depot (lanreotide) Injection, all of which are also somatostatin analogs. Proposed advantages to the pasireotide formulation include a higher binding affinity to all five somatostatin receptors, as well as a more pronounced IGF-1 suppression.

The sponsor intends to submit a new drug application (NDA) 203255 in April 2012, supported mainly by the pivotal clinical study C2305, entitled "A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly". The planned dosages are 20 mg, 40 mg and 60 mg, administered every 28 days.

Pasireotide received orphan designation on August 25, 2009, for the treatment of acromegaly.

On January 20, 2011, the sponsor submitted a request for review of its proposed proprietary name for this product, Signifor LAR. On July 19, 2011, a conditionally acceptable letter issued. The sponsor should submit a request for review of the proprietary name again once the NDA is submitted.

The sponsor submitted a Pre-NDA meeting briefing document on October 31, 2011. Preliminary responses were sent to the sponsor via secure e-mail on November 23, 2011.

2.0 DISCUSSION

Novartis' questions and pre-meeting follow-up responses appear in regular text. **FDA preliminary responses appear in bold, regular text. Meeting discussion and FDA post-meeting comments are shown in bold, italic text.**

QUESTIONS FOR THE AGENCY

Quality

Question 1: Substantiation and verification of selected (b) (4)

Pasireotide (SOM230) powder for suspension for injection in vials is (b) (4)

(b) (4) For validation of the process, the (b) (4) method is applied.

Novartis is seeking agreement on the interpretation of the (b) (4) guidance with regard to substantiation and verification of the selected (b) (4).

Does the Agency agree with the approach below?

FDA Preliminary Response: The dose audit substantiation of the (b) (4) Due to the expected very low bioburden of the drug product, detailed descriptions of the methodology (for example, most probably number, plate count, etc) used for this in-process bioburden testing will be expected at the time of NDA submission. Overall, the proposed control/dose auditing procedure is acceptable.

You stated that you would file a comparability protocol for the repeat dose substantiation process (including adaptation of bioburden action limit) within the original NDA 203255 submission. You propose a filing strategy of CBE-0 following the successful completion of the comparability protocol. Should your comparability protocol receive approval, you are advised to contact the review Division prior to filing any subsequent change supplement resulting from the implementation of that comparability protocol since opportunities for regulatory discretion exist which could result in a possible downgrade of the filing category. However, from a microbiology product quality perspective, your proposal would be considered one of the acceptable options.

Meeting Discussion: Refer to slide 15 of sponsor slide presentation. FDA stated that the sponsor's response was acceptable regarding the in-process bioburden testing methodology. FDA also emphasized that the sponsor's bioburden sampling plan should be robust since potential microbial contaminants may not be uniformly distributed across the batch. The sponsor should consider multiple sampling points throughout the fill. Since the bioburden is expected to be very low, a composite of 10 units/sampling point is suggested. The sponsor replied that it will consider these points in its bioburden testing. FDA also pointed out that the proposed comparability protocol (CP) would be specific for this product presentation only, and that any deficiencies identified in the CP would be no different than any other CMC deficiency as it relates to approvability of the NDA submission.

Question 2: Data package to support the commercial presentation

Pasireotide LAR is formulated as a powder for suspension for injection, and will be provided as 20 mg, 40 mg, and 60 mg vials and 2 mL vehicle in prefilled syringes and vial adapter in the commercial presentation. In the pivotal clinical study for the treatment of acromegaly all 3 strengths were tested. The vehicle was provided in ampoules in the clinical presentation. To achieve 60 mg in the clinical study, one 20 mg and one 40 mg vial were pooled in 2 mL vehicle.

Does the Agency agree that the proposed data package detailed below in support of the commercial presentation is adequate?

FDA Preliminary Response: Your proposed drug product commercial presentation appears adequate for filing. The packaging and stability data will be reviewed after the application is filed. We have the following comments for your consideration as the NDA application is prepared:

- a. **Demonstrate that 2 mL diluent is sufficient to resuspend all three dose strengths of pasireotide LAR powder. When injecting the different dose strengths, do some of the dose strengths congeal and clog the needle sooner than other dose strengths? Does this have a practical impact on administration of different dose strengths?**
- b. **Confirm that all manufacturing and testing facilities are listed in your application and are ready for inspection at the time of NDA filing.**

Meeting Discussion: None; sponsor accepts FDA Preliminary Response. Refer to slide 16 of sponsor slide presentation.

Nonclinical

Question 3: Non Clinical Program

An extensive non-clinical program was conducted with pasireotide. Does the Agency agree that:

- a) the toxicology package is adequate to meet regulatory requirements for the nonclinical evaluation of pharmaceuticals for human use and to support registration of the pasireotide LAR formulation in acromegaly?

FDA Preliminary Response: Based on the description in your briefing document, your nonclinical program for the pasireotide LAR formulation seems adequate for NDA filing.

Meeting Discussion: *None; sponsor accepts FDA Preliminary Response.*

b) the impurities/degradants for the final clinical formulation have been qualified?

FDA Preliminary Response: **The impurity/degradant profiles in drug substance and drug product appears adequately identified, qualified, and within limits of ICHQ3, based on the description in your briefing document from a pharmacology/toxicology perspective.**

Meeting Discussion: *None; sponsor accepts FDA Preliminary Response.*

Clinical Pharmacology

Question 4: Clinical Pharmacology Program

An extensive Clinical Pharmacology (CP) program was conducted for both the pasireotide s.c. formulation and LAR formulation. Considering that pasireotide is the same active entity in both formulations, the results from the s.c. formulation can be bridged to further support the available CP data from the LAR formulation.

The current CP package including two TQT studies conducted with the s.c. formulation, a hepatic impairment study conducted with the s.c., formulation, and renal Pop PK/PD with LAR data from phase III study C2305, is considered sufficient and adequate to support registration of pasireotide LAR in acromegaly.

Does the Agency agree?

FDA Preliminary Response: **Generally, the clinical pharmacology package appears to be reasonable to support the filing of pasireotide LAR in acromegaly. The adequacy of the data will be a review issue.**

Your plan to evaluate the effect of renal impairment on pasireotide LAR by population pharmacokinetic/pharmacodynamic (PK/PD) approach based on data from Phase 3 trial C2305 in acromegaly patients is acceptable. However, in order to obtain reliable information on the effect of renal impairment on pasireotide pharmacokinetics, adequate number of patients in each renal impairment category is needed.

Clarify whether the to-be-marketed formulation is identical to the formulation used in clinical development. If not, a bridging study will be needed.

Please note that the data included in the two thorough QT study reports submitted to IND 068635 (pasireotide s.c. formulation) on November 2, 2011, is being reviewed by our QT Interdisciplinary Review Team and feedback will be provided after this meeting, either in post-meeting comments or in a separate letter.

Meeting Discussion: Refer to slides 4-5 of sponsor slide presentation. The sponsor sought agreement from FDA that the completeness of the Clinical Pharmacology package is not affected by the forthcoming review by the QT-Interdisciplinary Review Team (IRT). FDA confirmed that this is correct and that the appropriate findings will be reflected in the labeling during the NDA application review. The anticipated review completion date by the QT-IRT is December 30, 2011.

Question 5: Pooling strategy for data analyses in support of the Summary of Clinical Pharmacology

The following pooling strategy for data analyses will be performed in support of the Summary of Clinical Pharmacology (SCP). Does the Agency agree?

FDA Preliminary Response: Your pooling strategy for data analysis in support of the summary of clinical pharmacology is acceptable.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Clinical Safety and Efficacy

Question 6: Registration trial and proposed indication

The application will be based primarily on the data from the Phase III registration trial C2305 performed with the LAR formulation in patients with acromegaly. The data consist of the 12 months core phase data for SSA treatment naïve patients in comparison to octreotide (superiority design) and in addition data of at least 6 months of treatment in the extension phase including patients staying on the same treatment and patients crossing over to the other treatment in case of inadequate response to the prior SSA treatment. Novartis considers that this is a robust data package which adequately supports the intended proposed indication “treatment of patients with acromegaly (b) (4)”. Does the Agency agree?

FDA Preliminary Response: The data package appears acceptable. Since surgery is first-line therapy for the treatment of acromegaly and because the pivotal trial excluded subjects who previously received somatostatin analogues, pasireotide LAR should be more specifically indicated for “the long-term treatment in acromegalic patients who have had an inadequate response to surgery and/or for whom surgery is not an option”. Labeling should also state that the pivotal trial excluded patients who previously received other acromegaly medical therapies or radiotherapy. Please note these are preliminary comments on labeling based on information available at this time. Final labeling comments will accompany a review of your NDA.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response. Additional comments are on slide 18 of sponsor’s presentation.

Question 7: Completeness of clinical data

The clinical studies included in this application for pasireotide LAR in the treatment of acromegaly fulfill the available guidance and FDA advice received. Does the Agency agree that the proposed clinical content of the application is adequate to support the filing for pasireotide LAR in the treatment of patients with acromegaly?

FDA Preliminary Response: Overall, it appears that the proposed clinical content is adequate. You recently submitted a Safety Information Amendment after identifying several Hy's law cases associated with the s.c. formulation. Apart from Hy's law cases, for the meeting please comment on general drug-induced liver events associated with the LAR formulation. In the NDA, the Division expects a comprehensive report of hepatic safety that covers both the s.c. and LAR formulations in all trials performed (include all indications and healthy volunteers). For the meeting, specify planned analyses to detect drug-induced liver injury. For suggested analyses of liver tests, please refer to the Guidance for Industry: Drug-Induced Liver Injury. Additional analyses may be needed after the initial review. Analyses of transaminase marked abnormalities by treatment group should include the following categories: >3x, 5x, 10x, 20xULN.

Meeting Discussion: Refer to slides 6-10 of sponsor slide presentation. FDA asked what happened when patient CSOM230D2203 who had elevated ALT/AST and bilirubin levels was de-challenged. The sponsor replied that the liver function test remained high (i.e., no change).

Regarding the sponsor's planned dedicated hepatic report for the NDA submission (refer to slide 10), FDA asked if baseline hepatitis profiles were obtained for all patients. The sponsor replied that these were obtained for some, but not all, patients; follow-up hepatitis profiles were obtained once liver abnormalities were observed. Profiles were not obtained for the 3 observed Hy's law cases, as there was no mandated protocol to require them. FDA asked the sponsor to indicate in the NDA submission the reason why additional laboratory work-up was performed in some patients and not in others. The sponsor agreed, stating that full narratives would be provided, including a timeline, what happened and why.

Question 8: Data Pooling in support of Summary of Clinical Safety and Summary of Clinical Efficacy

Novartis considers that no pooling of efficacy or safety data is required for the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS). Does the Agency agree?

FDA Preliminary Response: Yes. However, discussions of important safety issues, such as hepatic events, should include subjects in all trials and all indications.

Meeting Discussion: Refer to slide 11 of sponsor slide presentation. The sponsor confirmed that it would not be pooling efficacy and safety data. FDA agreed that this is acceptable.

Question 9: Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)

Does the Agency agree to the proposed approach to satisfy the requirements for an ISE and an ISS?

FDA Preliminary Response: Yes.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Question 10: Statistical Analysis Plan

Does the Agency agree that the statistical analyses for the pivotal phase III study (especially with regard to analyzing the “up to crossover” and ‘after crossover’ data separately and the analyses to be performed based on the after crossover data) is adequate to support the filing of the application?

FDA Preliminary Response: Yes. We concur with the statistical analysis plan for the primary endpoint (evaluated at Month 12 of the core period), for endpoints measured during the core period, and for endpoints measured during the extension period. This concurrence references the Report Analysis Plan (RAP), Amendment 3. Specifically, we concur with (1) the definitions of the analysis sets; (2) the classification rules for the Month 12 endpoint regarding patients who discontinued prior to that time; (3) the statistical methods described for the primary efficacy endpoint, including the primary method and the sensitivity analysis; (4) the analysis plan for the secondary efficacy endpoints measured in the core phase, including the protection of Type I error for key secondary efficacy variables; and (5) the analysis plan for variables measured during the extension period, which consists entirely of descriptive and summary statistics.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Question 11: Case Report Forms/Patient Narratives/Patient Profiles

- a) Does the Agency agree that the Novartis proposal detailed below will fulfill the NDA review requirements with respect to CRFs and patient narratives?

FDA Preliminary Response: Yes.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

- b) Novartis is planning to submit patient profiles for all C2305 patients. Does the Agency agree to the proposed format attached to this Briefing Book?

FDA Preliminary Response: Yes. Ensure that study drug dose increases are included in the profile. Please group the profiles by treatment arm, as well as those who continued in the extension phase, and by crossover status.

Meeting Discussion: *None; sponsor accepts FDA Preliminary Response.*

Question 12: 120 Day Safety Update

Does the Agency agree to the content of the 120 day safety update?

FDA Preliminary Response: **Yes.**

Meeting Discussion: *None; sponsor accepts FDA Preliminary Response.*

Question 13: Case Report Tabulations (CRT) requirements and SAS Programs for Analysis and Datasets

Novartis intends to submit CRTs for all Clinical Pharmacology studies and for all phase II and phase III studies performed in the claimed indication (acromegaly). Novartis does not plan to provide safety and efficacy CRTs for studies conducted in carcinoid or Cushing's disease patients. In addition, Novartis plans to provide the analysis programs for the analysis of the primary and key secondary efficacy endpoints, along with the programs used to generate the derived efficacy datasets for the pivotal phase III study C2305. Does the Agency agree this plan satisfies the requirements of 21 CFR §314.50(f)(1)?

FDA Preliminary Response: **Yes.**

Meeting Discussion: *None; sponsor accepts FDA Preliminary Response.*

Question 14: Risk Management

Novartis global Risk Management Plan (RMP) contains a thorough analysis of the risks associated with the intended use of pasireotide LAR and proposed risk management options. The risks can be managed by appropriate labeling and routine pharmacovigilance activities that are outlined in the RMP. Given that the safety risks identified by Novartis are generally common to the SAA class of drugs, Novartis proposes to submit a RMP instead of a REMS for NDA 203255 (pasireotide LAR). Does the Agency agree?

FDA Preliminary Response: **A complete review of the full risk management plan after the NDA is submitted will be necessary to determine whether it is acceptable, and whether a Risk Evaluation and Mitigation Strategy will be necessary to ensure that the benefits of the drug outweigh the risks of the drug.**

Meeting Discussion: *Refer to slide 12 of sponsor slide presentation. The sponsor stated that it plans resubmission of NDA 200677 (SOM230B pasireotide s.c. for the treatment of Cushing's disease) in January/February 2012, and submission of NDA 203255 (SOM230C pasireotide LAR) around April 2012. The sponsor will also be requesting priority review and inquired as to what would be the timelines for RMP assessment in the case of priority review being granted. FDA reminded the sponsor that a standard NDA review is 10 months, while a priority review is 6 months. For a 6-month priority review,*

risk management (including REMS) information is communicated to the sponsor shortly after FDA's internal meeting at month 5.

Regulatory/Administrative

Question 15: Overall Content of the NDA

Does the Agency agree that the content described in the draft NDA Table of Contents together with the information provided in this briefing document is acceptable to support a complete NDA?

FDA Preliminary Response: Yes.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Question 16: User fee and pediatric waiver based on orphan designation

Based on the Orphan designation Novartis received for pasireotide for the treatment of acromegaly:

- a) A user fee waiver is not required
- b) A pediatric waiver is not required

Does the Agency agree?

FDA Preliminary Response: Yes. A user fee is not required for, and PREA is not triggered by, orphan drug applications. However, the standard user fee cover sheet Form 3397 should be included in your NDA submission.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Question 17: Financial disclosure

Novartis considers studies C2305, B2216, B2113, B2124 and B2125 covered by the rule "Financial Disclosure for Clinical Investigators". Does the Agency agree that these are the only "covered studies"?

FDA Preliminary Response: Yes.

Meeting Discussion: None; sponsor accepts FDA Preliminary Response.

Question 18: Cross-referencing to NDA 200667

Study reports (preclinical, clinical pharmacology, and clinical) as well as certain CRTs, CRFs, and financial disclosures which support this application may have already been submitted with NDA 200667 at the time NDA 203255 is submitted. In this situation

Novartis does not plan to resubmit the previously submitted information in NDA 203255, but proposes to cross-reference to NDA 200677 instead.

- a) Does the Agency agree to the proposal to cross-refer to an application that is still under review by the Division?
- b) Does the Agency agree with the proposed cross-referencing plan as detailed below?

FDA Preliminary Response: Yes.

Meeting Discussion: Refer to slide 13 of sponsor slide presentation. The sponsor stated that submission of NDA 203255 (acromegaly indication) is planned to occur after the resubmission of NDA 200677 (Cushing's syndrome indication). NDA 203255 will cross-reference some information from NDA 200677. Given that NDA applications must be complete at the time of submission, the sponsor expressed concern about how NDA 203255 may be impacted in the event that a refuse-to-file (RTF) decision were to be made for NDA 200677. The sponsor reminded FDA that the CMC and nonclinical sections of NDA 203255 will be complete, and the only potential missing items (if a RTF decision was made for NDA 200677 and thus the NDA could no longer be cross-referenced) would be toxicology Clinical Study Reports (CSRs), clinical CSRs and datasets. FDA replied that in such an event these items could be submitted via an amendment to NDA 203255 in a timely manner before the filing meeting is scheduled to take place.

Additional FDA Comments

Office of Scientific Investigations (OSI)
See attachment at the end of this document.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

- Slides presented by Novartis Pharmaceuticals Corp. at Type B Pre-NDA Meeting
- Requests from the Office of Scientific Investigations (OSI)

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The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

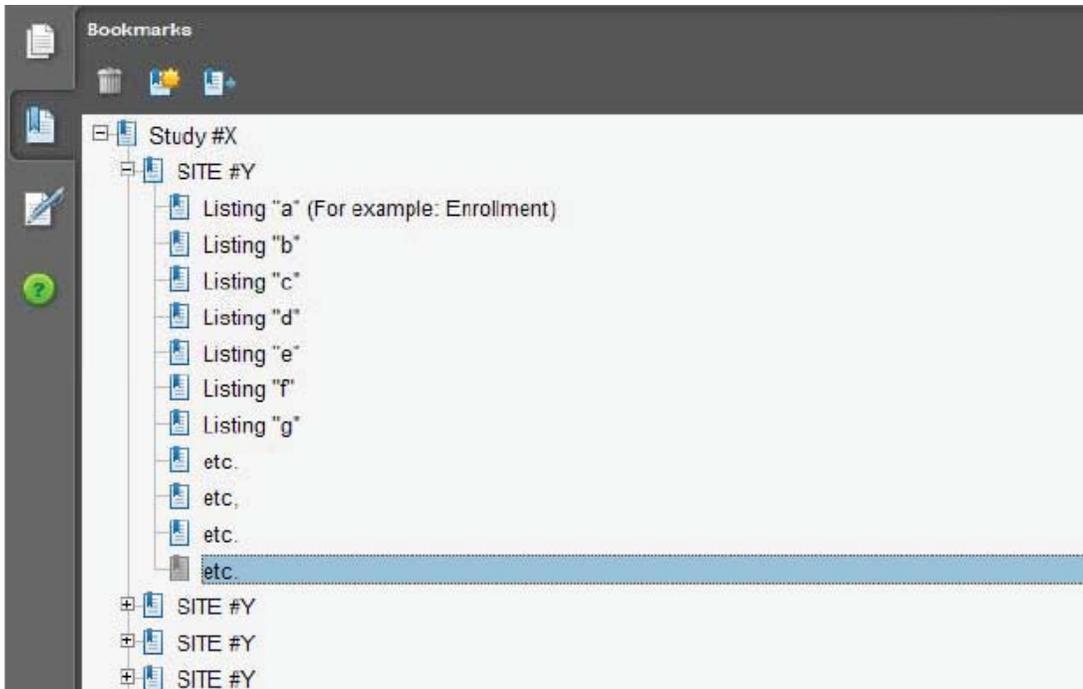
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials.
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies.
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
6. For each pivotal trial, if applicable, provide the data monitoring committee charter and steering committee charter.
7. A summary of GCP deficiencies identified at each site that has been closed by Novartis due to identification of serious GCP violations (i.e., two sites in Mexico identified in Pre-NDA meeting package and any additional site that is subsequently identified at which serious GCP deficiencies have been identified that the sponsor determines impact reliability of data submitted in the NDA).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization) for core phase of study.
 - c. Subject listing for treatment assignment for extension phase of study.
 - d. Subject listing of drop-outs and subjects that discontinued with date and reason
 - e. Evaluable subjects/ non-evaluable subjects and reason not evaluable
 - f. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - g. By subject listing, of AEs, SAEs, deaths and dates
 - h. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - i. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - j. By subject listing of concomitant medications
 - k. By subject listing, of laboratory tests, gallbladder ultrasound results, and ECG results performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR.”

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

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Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

JENNIFER L JOHNSON
12/20/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 74,642

Novartis Pharmaceuticals Corporation
Attention: Jason Kraker, M.S.
Senior Manager, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Kraker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOM230C LAR (pasireotide) Injection.

We also refer to the meeting between representatives of your firm and the FDA on October 15, 2007. The purpose of the meeting was to discuss your proposed Phase 3 drug development program for acromegaly.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Phase 2 Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 15, 2007
TIME: 11:30 am – 1:00 pm
LOCATION: Teleconference
APPLICATION: IND 74,642
DRUG NAME: SOM230C LAR (pasireotide) Injection
TYPE OF MEETING: Type B: End-of-Phase 2

MEETING CHAIR: Mary H. Parks, M.D.

MEETING RECORDER: Jennifer Johnson

FDA ATTENDEES: (Title and Office/Division)

Mary H. Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Robert Perlstein, M.D.	Clinical Reviewer, DMEP
Karen Davis Bruno, Ph.D.	Supervisor, Pharmacology/Toxicology, DMEP
Dylan Yao, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Sally Choe, Ph.D.	Team Leader, Office of Clinical Pharmacology, Division of Clinical Pharmacology II (OCP/DCP2)
S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCP2
J.Todd Sahlroot, Ph.D.	Deputy Director and Team Leader, Office of Biostatistics, Division of Biometrics II
Janice Derr, Ph.D.	Biometrics Reviewer
Jennifer Johnson	Regulatory Project Manager, DMEP
Chris Holland, M.S.	Mathematical Statistician, Quantitative Safety and Pharmacoepidemiology Group

EXTERNAL CONSTITUENT ATTENDEES:

Representing Novartis Pharmaceuticals Corporation

Prem K Narang, Ph.D.	Vice President, Global Head of Drug Regulatory Affairs (DRA) Oncology
Jay Kraker, M.S.	Senior Manager, DRA
Pio Zapella, Ph.D.	Manager, DRA Oncology
Gabriela Gruia, M.D.	Group Leader, Clinical Development and Medical Affairs
Joan Glusman, M.D.	Clinical Program Leader
Mike Hu, Ph.D.	Clinical Pharmacologist
JinPing Wang, Ph.D.	Biostatistician
Michelle Tenerelli, Ph.D.	Project Manager
Maryelle Kolopp, M.D., Ph.D.	Toxicologist, Preclinical Safety

BACKGROUND:

Novartis Pharmaceuticals Corporation requested this Type B End-of-Phase 2 meeting and submitted a background package to discuss the Phase 3 drug development program for SOM230C LAR (pasireotide) Injection (an intramuscular depot). This somatostatin analog is a new molecular entity being developed to treat patients with acromegaly (b) (4).

Currently approved drug treatments for acromegaly include Sandostatin LAR (octreotide acetate) and Somatuline Depot (lanreotide), both of which are also somatostatin analogs. Proposed advantages to the pasireotide formulation include a higher binding affinity to all five somatostatin receptors, as well as a more pronounced IGF-1 suppression.

The Sponsor intends to submit a new drug application (NDA) following completion of Study C2305, entitled “A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs. octreotide LAR in patients with active acromegaly”, the design of which is the subject of this meeting’s discussion. The planned dosage is 60 mg, administered every 28 days.

MEETING OBJECTIVES:

To discuss the Sponsor’s proposed Phase 3 drug development program for SOM230C LAR (pasireotide) Injection for the treatment of acromegaly.

DISCUSSION POINTS:

Please note: The Sponsor’s questions are repeated below in regular type, followed by the Division’s response (bolded). Any documented discussion at the meeting and subsequent Division response is denoted in bold and italic type.

Non-clinical

Question 1

Does the Agency agree that the proposed preclinical safety program adequately supports the registration of pasireotide LAR in the proposed patient population at the foreseen maximum intramuscular (i.m.) dose of 60 mg every 28 days?

Toxicokinetic data comparing single dose LAR formulations 2 and 2b via an intramuscular route in rats and multiple dose rat toxicity data with formulation 2 appear to share a similar toxicology profile to immediate release SOM230, and an appropriate bridge from formulation 2b to previous SOM230 data can be made. It is unclear if qualification of impurities in formulation 2b has been addressed, as there does not appear to be any multiple dose toxicity studies with formulation 2b. Table 2-2 (pg 14) of the briefing document does not specify the formulation used for testing. Therefore, a repeat dose toxicity study in a single species of 4-week duration with formulation 2b (clinical formulation) is requested in addition to in vitro genotoxicity testing to qualify any impurities or degradants.

During the meeting the Sponsor provided additional information regarding Nonclinical Question 1, which included a table with degradation products-batch analysis results and suggested that the impurity profiles of Formulation 2 and 2b were equivalent. Furthermore, Novartis suggested that given the similar impurity profile, impurities in Formation 2b are considered to be qualified by studies using a drug batch enriched with impurities from Formulation 2 ("Tox 3"). These studies, which include a 4-week repeat dose toxicity study and genotoxicity studies, are completed but the report has not been submitted for review.

Clinical

Question 2

Novartis considers the proposed 'inclusion and exclusion' criteria for study C2305 to be adequate to define the target population to assess the safety and efficacy of pasireotide LAR in the treatment of patients with acromegaly (b) (4). Does the Agency agree?

Your proposal to study acromegalic patients naïve to pharmacologic agents who 1) have undergone resection of the pituitary adenoma; or 2) are *de novo* to medical and surgical therapies is acceptable. However, we also recommend the following modifications to your patient selection criteria:

- **Exclude any patient who has received pituitary irradiation. The long-term effects of radiation therapy on GH secretion may confound the results of this study.**
- **For patients in Stratum 1 (previous pituitary surgery), evaluation of the resected adenoma with respect to receptor subtype is recommended.**
- **We agree with the exclusion of diabetics with hemoglobin A1c values > 8%. However, we strongly recommend the following with regard to the monitoring of glucose tolerance on-study:**
 - **Patients with preexisting diabetes mellitus should be monitored very carefully while on-study including frequent home blood glucose monitoring (at least twice a day), monthly determinations of fasting blood glucose (FBG) in the laboratory, and hemoglobin A1c levels every 3 months. An investigator experienced in the management of diabetes mellitus should interface with these patients frequently and adjust their therapeutic regimens as necessary to 1) avoid deterioration of diabetic control secondary to study drug exposure; and 2) optimize diabetic control. Information regarding any changes in anti-diabetic therapy (i.e., changes in oral agent regimen, initiation of insulin, dose increases or decreases of oral agents and/or insulin) should be comprehensively summarized in the NDA submission. Patients who develop symptoms of diabetes mellitus out of control and/or blood glucose values consistently in excess of 200 mg/dL in spite of appropriate therapeutic interventions should be discontinued from the study, as should patients whose hemoglobin A1c values exceed 8%.**
 - **Shift tables at multiple time points should be presented for patients with normal FBG at baseline (<100 mg/dL) or impaired fasting glucose (IFG) at baseline (100-125 mg/dL), i.e., the number of patients who "shift" from normal FBG at baseline to IFG or overt diabetes mellitus (FBG ≥126 mg/dL)**

at any given time point, and the number of patients who “shift” from IFG at baseline to overt diabetes mellitus at any given time point.

- All patients should undergo or should have recently undergone appropriate testing to rule out central hypothyroidism, central hypoadrenalism, central hypogonadism and diabetes insipidus. Patients with confirmed central hypothyroidism, central hypoadrenalism and diabetes insipidus should not be enrolled in the trial until they have been adequately treated with stable doses of hormone replacement therapy for a minimum of three months.

Question 3

Novartis considers that the proposed definition of responder, as well as the primary and secondary endpoints and analysis plan of study C2305 are adequate to establish the efficacy of pasireotide LAR in the studied population. Does the Agency agree?

Responder as defined by mean 5-point GH and/or IGF-1 levels is acceptable; however, please provide a rationale for evaluating GH response based on the mean value of a 5-point profile within a 2 hour time period in lieu of a GH level 2 hours after a 75 g glucose load. In addition, in your Phase 1 and 2 studies in acromegalic patients, you presented data that suggest that the number/percentage of patients with mean 5-point GH levels <2.5 ng/mL is dependent upon Baseline GH levels. Small differences in Baseline GH levels may affect this primary efficacy endpoint, and we therefore emphasize the importance of a valid randomization method for allocating patients between the two treatment arms. Analyses of GH as a continuous variable may include baseline GH level as a covariate.

We view all but the GH and IGF-1 secondary endpoints as exploratory. Consequently, the effects of SOM230 on these endpoints may not be discussed in labeling.

Question 3: Discussion at the meeting following receipt of written response by the Sponsor to the Division’s written response above:

After some discussion, the Division strongly recommended that the Sponsor consider adding the GH level 2 hours after a 75 g glucose load as an additional efficacy endpoint in a substantial subset of patients enrolled by participating sites in the United States. The Division indicated that this would not be a mandatory change to the protocol. The Sponsor agreed to consider this recommendation.

Question 4

Does the Agency agree that the proposed duration of 6 months is adequate to assess the efficacy of pasireotide LAR in the studied population?

No. To date, SSA approval studies have had a minimum duration of one year for efficacy evaluation. Your selection of 6 months may be an adequate time point for steady state pharmacokinetics, but may not be adequate to establish efficacy in both treatment groups. Furthermore, if this pivotal study will form the basis for your claiming superiority (or non-inferiority) to an established therapy, a minimum of one year duration is necessary to evaluate both the efficacy and safety of the two products.

Question 5

Novartis considers it appropriate to have octreotide as the comparator arm in study C2305. Does the Agency agree?

You are not required to have a comparator arm, as other SSAs have been approved based on open label, baseline-controlled studies. For this disease, it is not expected that patients will experience spontaneous remission or improvements of the excessive GH/IGF-1 secretion. If you choose to have an octreotide LAR comparator arm as proposed in your protocol, the trial must be of one year duration and the aim of the study should be to demonstrate superior efficacy of pasireotide LAR over octreotide LAR.

Questions 4 and 5: Discussion at the meeting following receipt of written responses by the Sponsor to the Division's written responses above:

The Sponsor suggested various ways in which the results of a 6-month trial could be used to support registration. The Division made it emphatically clear that a study of 1 year duration would be required whether the sponsor 1) decides to include an octreotide LAR comparator arm (i.e., to demonstrate the superior efficacy and safety of pasireotide LAR over octreotide LAR) or 2) conducts a baseline-controlled, single arm study. All 1 year efficacy and safety results should be included in the initial NDA submission.

Question 6

Does the Agency agree that the doses of pasireotide and octreotide selected for study C2305 are appropriate?

Yes. Your rationale in selecting the doses for Study C2305 via comparing trough concentrations at different doses from the Phase 1 pasireotide LAR 2110 study with the predicted median $C_{\text{effective}}$ from the Phase 2 pasireotide SC 2201 study seems reasonable. The $C_{\text{effective}}$ should be confirmed when all of the data from the Phase 1 pasireotide LAR 2110 study have been collected.

Question 7

Novartis believes that enrollment of 330 patients in study C2305 is adequate to detect the treatment difference between the pasireotide and octreotide arms. Does the Agency agree?

We agree with the statistical calculations that you provided to support the enrollment of 330 patients, 165/arm, in Study C2305.

Clinical Pharmacology

Question 8

Novartis believes that the proposed Clinical Pharmacology Development Plan is adequate to support the filing of pasireotide LAR. Does the Agency agree?

In general, pasireotide LAR's Clinical Pharmacology Development Plan is acceptable. However, you should consider conducting the following:

- a renal impairment study for pasireotide in acromegalic patients
- an interaction study between pasireotide and cyclosporine

Question 9

Reference is made to our briefing package dated April 14, 2006 and EOP2 meeting with the Agency on May 15, 2006 during which we discussed our clinical development program for pasireotide s.c. for the treatment of Cushing's disease, including the design of the thorough QTc

study. Reference is also made to the minutes of the meeting dated June 5, 2006 (see [Appendix 9](#)) in which FDA disagreed with the single dose design and recommended "*multiple doses for the QT study using the highest tolerable dose with BID regimen to reach a steady state exposure for QT assessment*". Based on FDA's recommendation, Novartis has revised the design of the QTc study CSOM230B2113 (B2113) to employ a multiple b.i.d. dosing regimen for 5 days in both stages of the study, and starting at 750 µg b.i.d. in Stage I. For more detailed information on the study design, please refer to the study outline ([Appendix 7](#)).

- a) Does the Agency agree with the proposed starting dose of 750 µg pasireotide s.c. b.i.d. and dose escalation strategy in Stage I?
- b) Novartis believes that the criteria set for Stage I to determine the dose to be tested in Stage II of the study are appropriate. Does the Agency agree?
- c) Novartis believes that the design of the thorough QTc study adequately assesses the potential for QTc prolongation of both pasireotide s.c. and pasireotide LAR. Does the Agency agree?

In general, your approach to the thorough QTc study seems reasonable. However, you should submit Study CSOM230B2113's protocol to the Division to be reviewed by the Interdisciplinary Review Team (IRT) for further comments before starting the study.

ATTACHMENTS/HANDOUTS:

- PowerPoint slides and drug impurities table presented by Sponsor
- Comments to Sponsor from the Quantitative Safety and Pharmacoeconomics Group (Office of Biostatistics, Division of Biometrics IV)

Minutes prepared by: Jennifer Johnson
Chair Concurrence: Mary Parks

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Quantitative Safety and Pharmacoepidemiology Group
Pasireotide End of Phase II Package
Comments on the Safety Analysis Plan in the Protocol for Study C2305

1. Introduction

Pasireotide is an injectable somatostatin analogue. It is being investigated as a once-a-month intramuscular depot injection (pasireotide LAR) for the treatment of acromegaly, a rare, seriously debilitating condition characterized by chronic hypersecretion of GH (growth hormone).

On September 20, 2007, the sponsor of pasireotide submitted a briefing book to FDA in preparation to a Type B, End of Phase II Meeting scheduled for October 15, 2007. The Quantitative Safety and Pharmacoepidemiology Group (QSPG) in the Office of Biostatistics was consulted to provide comments on the briefing book and proposals relating to planned analyses and the collection of safety data.

Section 2 of this memo contains specific comments relating to the proposed safety analysis provided in the draft protocol for Study C2305. Appendix 1 of this memo contains the standard data request formulated by the QSPG. It contains information relating to the structure and content of the data sets submitted to FDA as part of an NDA or BLA submission. It also contains a request for a quantitative safety analysis plan and its important components.

2. Comments on the Proposed Safety Analysis for Study C2305

1. Section 10.5.3.1 describes the proposed summaries of adverse events. It states:
All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, severity (based on CTC grades), type of adverse event, relation to the study drug by treatment group. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group. Injection site reactions will be specifically identified and summarized by treatment group.

Please ensure that the verbatim term for adverse events are captured and included in the submitted data sets and that this term is used for MedDRA coding. In addition to the tables that summarize adverse events by the Preferred Term and System/Organ/Class, please also consider summaries at the High Level Term and High Level Group Term level. Please use Standardized MedDRA Queries (SMQs) for your AE analysis. The inclusion of mock table shells for all unique layouts of AE summaries will help with the evaluation of your safety analysis plan.

Please identify adverse events of special interest (AESIs) using all available sources of information (e.g. pre-clinical studies, PK studies, etc.). Provide details

of how AESIs will be assessed in the Quantitative Safety Analysis Plan (QSAP). Consider time-to-event analyses of AESIs including a detailed description of how these analyses would be performed.

2. Section 10.5.3.2 describes the proposed summaries of laboratory abnormalities. It states:

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTC). Blood glucose will be presented as mg/dL and will be assessed using the ADA criteria 2004.

A listing of all laboratory values will be provided by laboratory parameter, patients, and treatment group. A separate listing will display notable laboratory abnormalities (i.e. newly occurring CTC grade 3 or 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by parameter and treatment group. Laboratory data will be summarized by presenting shift tables using CTC grades.

Please describe how patients with laboratory abnormalities will be managed. Ensure that all laboratory data, including unscheduled laboratory data, are provided in the submitted data sets. Use all laboratory data for summaries and analyses where appropriate. For example, when unscheduled labs occur within a given window of time around a scheduled visit, they should be considered for summaries at those visits. Please provide change from baseline analyses of all laboratory parameters using the most recent value prior to the start of study medication as the baseline value. For the listing of laboratory abnormalities, include newly occurring CTC grade 2 laboratory toxicities and ensure that abnormal values from unscheduled labs are listed as well.

3. Section 10.5.3.3 describes the proposed summaries of “other safety data”. It states:

Data from other tests (e.g., vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

ECG data will be summarized at baseline and post-dose time point. Change from baseline ECG data will also be summarized. Number and percentage of patients with clinically notable values will be calculated at each time point.

Gallbladder data at each visit will be summarized and listed by treatment group.

Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

Please list and reference the criteria to be used to identify “notable” vital sign values, in particular, blood pressure endpoints. In addition to the listings of notable vital sign values, please perform change from baseline analyses of your

vital sign data (blood pressure, heart rate, and body temperature) at each visit where vital signs are collected using two different reference points as the baseline: 1) the pre-dose Visit 2 measurement and 2) the pre-dose measurement from each visit. Appropriate statistical tests of these results may be performed in order to highlight findings.

Appendix 1

Safety Analysis Plan and Data Request to Sponsors

CDISC Data Requests to Sponsors Quantitative Safety and Pharmacoepidemiology Group

Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).

At a minimum the Safety Analysis Plan should address the following components:

- Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).
- Safety endpoints for Adverse Events of Special Interest (AERI)
- Definition of Treatment Emergent Adverse Event (TEAE)
- Expert adjudication process (Expert Clinical Committee Charter)
- Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
- When unanticipated safety issues are identified the QSAP may be amended.

Study Data Tabulation Model (SDTM) Issues

1. The current published SDTM and SDTM Implementation Guide (SDTMIG) should be carefully followed.
 - a. Refer to the SDTMIG section on Conformance (3.2.3)
2. Domains
 - a. There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, please use these domains.
 - i. (DV) Protocol deviations
 - ii. (DA) Drug Accountability
 - iii. (PC, PP) Pharmacokinetics
 - iv. (MB, MS) Microbiology
 - v. (CF) Clinical Findings
 - b. The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.
 - i. Tumor information
 - ii. Imaging Data
 - iii. Complex Inclusion/Exclusion Criteria

3. Variables

- a. All required variables are to be included and populated.
- b. All expected variables should be included in all SDTM datasets.
- c. Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the review division.
- d. A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the review division.
- e. A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.
- f. Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.

4. Specific issues of note:

- a. SDTM formatted datasets should not provide replication of core variables (such as treatment arm) across all datasets, unless specified by the SDTM standard.
- b. Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.
- c. These issues can be addressed through the request for ADaM datasets

Analysis Data Model (ADaM) Issues:

1. Please specify which ADaM datasets you intend to submit.
2. Please include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.
3. Please discuss the structure of the datasets with the reviewing division and specify in the QSAP.
4. Within each adverse event analysis dataset, please include all levels of the MedDRA hierarchy as well as verbatim term.
5. Please indicate which core variables will be replicated across the different datasets, if any.
6. SDTM and ADaM datasets should use the same unique subject ID (USUBJID). Each unique subject identifier should be retained across the entire submission.

General Items:

1. Controlled terminology issues
 - a. Please use a single version of MedDRA for a submission.
 - i. Does not have to be the most recent version
 - b. We recommend that the WHO drug dictionary be used for concomitant medications.
 - c. Please refer to the CDISC terminology for lab test names.
 - d. Issues regarding ranges for laboratory measurements should be addressed.

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
11/9/2007 01:40:57 PM